

# Challenging Cases in Neonatology

**CASES FROM NEOREVIEWS™**  
**INDEX OF SUSPICION IN THE NURSERY**  
**AND VISUAL DIAGNOSIS**

**EDITORS**  
**DARA BRODSKY, MD, FAAP**  
**JOSEF NEU, MD, FAAP**



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American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



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# Preface

We are honored to edit this first edition of *Challenging Cases in Neonatology*. Our motivation for creating this book was prompted by the excellent contributions previously published in the Visual Diagnosis and Index of Suspicion in the Nursery sections in *NeoReviews*. We thought that this collection of articles would summarize the most interesting and important cases that have been published since 2004.

For this book, we selected cases using the following criteria: particularly challenging diagnoses, common problems with controversial treatments, and rare clinical presentations. In cases with outdated diagnostic or treatment modalities, we added commentaries to provide more-recent information from the literature. When possible and if relevant, the original authors also provided updates about the clinical course of the patients.

Of course, a book such as this one would not be possible without the assistance of many talented people. First, we would like to acknowledge the tremendous efforts of the authors who contributed to the original articles. We would also like to thank the following people: Alistair Philip (editor in chief of *NeoReviews* at the time of these publications) for his tremendous leadership, Joseph Puskarz (director of journal publishing, American Academy of Pediatrics [AAP]) for his thoughtful oversight, Luann Zanzola (managing editor, *NeoReviews*) for her valuable guidance, and Sara Strand and Lawanda Tucker (editorial associates, *NeoReviews*) for their dedication and hard work. Thanks also to Peter Lynch (manager, digital strategy and product development, AAP) and Evonne Acevedo (editor, digital publishing, AAP) for their significant contributions to the editing of this book. Finally, all this would not be possible without the strength of our patients and commitment of their families; they continue to motivate us to improve our clinical and diagnostic skills.

We hope that clinicians will enjoy reading this book and will gain knowledge that might be helpful at the bedside, when they are faced with similar clinical presentations.

Dara Brodsky, MD  
Joe Neu, MD

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*Part 1*

# **Cardiology**



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# Inconsolable Crying While Feeding

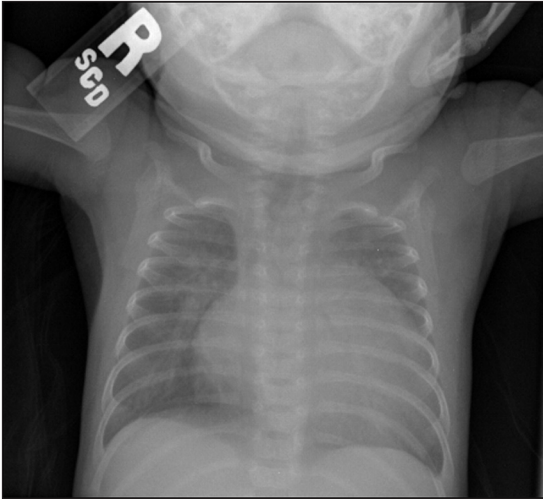
## Presentation

A nurse in the neonatal intensive care unit reports that a 5-week-old male infant has tachypnea. He has had acute episodes of irritability while being fed formula for the past week. He had been delivered by cesarean section because of late fetal decelerations at 29 weeks' gestation. At birth, he had mild respiratory distress syndrome that required bubble continuous positive airway pressure for 48 hours. He initially received intravenous fluids and gradually was started on feedings. Despite receiving full nipple feedings for the past week, he has not gained weight appropriately. The fussiness while feeding initially had been attributed to gastroesophageal reflux.

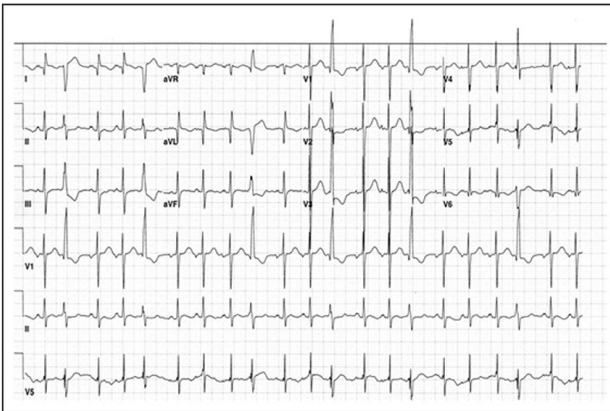
On physical examination today, the infant's temperature is 36.5°C, heart rate is 178 beats/min, respiratory rate is 76 breaths/min, blood pressure is 56/28 mm Hg, and oxygen saturation is 98% on room air. His weight is 2 kg, length is 42 cm, and head circumference is 30 cm. He has no obvious facial dysmorphisms. The capillary refill time is prolonged (5 sec), and he has feeble pulses, cool extremities, nasal flaring, and subcostal retractions.

Cardiac auscultation demonstrates a gallop rhythm and a 4/6 holosystolic murmur radiating to the left axilla. The liver is palpable 5 cm below the costal margin. Chest examination reveals bilateral rales. The remainder of the physical findings are unremarkable.

Complete blood count and metabolic profile yield normal results. Chest radiograph shows an enlarged cardiac silhouette (Figure 1.1). The infant's 12-lead electrocardiography (ECG) is shown in Figure 1.2. Further investigation confirms the diagnosis.



**Figure 1.1.** Chest radiograph showing cardiomegaly.



**Figure 1.2.** Electrocardiogram at age 5 weeks.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

### Diagnosis

The clinical diagnosis was congestive heart failure, and intravenous fluids and milrinone were initiated. Echocardiography revealed an enlarged, poorly contracting left ventricular chamber with an ejection fraction of 25% and a moderate degree of mitral valve regurgitation. The left atrium was enlarged, with bowing of the interatrial septum. A prominent right coronary artery originated from the right aortic cusp, with a smaller left coronary artery (LCA) arising from the pulmonary artery

(PA). Color flow imaging demonstrated retrograde flow into the PA. Based on these findings, the final diagnosis was left ventricular cardiomyopathy due to anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA).

### ***Differential Diagnosis***

The differential diagnosis of heart failure in an infant can be left-to-right shunts (ventricular septal defect), left-sided obstructive lesions, myocarditis, metabolic disorder (hypocalcemia), arrhythmias, arteriovenous malformation (vein of Galen, hepatic, pulmonary), coronary ischemia (ALCAPA, Kawasaki disease), or acute hypertension. Electrocardiography can help in delineating the cause of heart failure in infants.<sup>1</sup>

### ***The Condition***

Anomalous origin of the left coronary artery from the pulmonary artery may occur as an isolated defect or in association with other congenital heart defects such as patent ductus arteriosus, tetralogy of Fallot, or truncus arteriosus. It is also known as Bland-White-Garland syndrome. Its incidence is approximately 1 in 300,000 live births. Embryologically, ALCAPA results from abnormal septation of the conotruncus or abnormal persistence of pulmonary artery coronary buds and abnormal involution of aortic coronary buds.<sup>2</sup>

### ***Pathophysiology***

The clinical manifestations of patients who have ALCAPA usually are evident by 2 to 3 months of age. During the newborn period, there is antegrade blood flow from the PA to the LCA. Because pulmonary vascular resistance (PVR) is elevated in the neonate, myocardium supplied by the LCA is not ischemic, even though it is perfused by desaturated blood from the PA. As the PVR falls at around 6 to 8 weeks of age, flow to the LCA is severely compromised. To compensate, collateral anastomoses between right and left coronary arteries ensue. With further decline in PVR, blood flow reverses from the LCA into the PA. This phenomenon is known as coronary steal syndrome and results in myocardial ischemia. Mitral valve regurgitation is a frequent complication and is due to papillary muscle infarction and dilated mitral valve annulus.

### ***Clinical Presentation***

The initial symptoms of ALCAPA include poor feeding, pallor, and paroxysms of crying, irritability, or diaphoresis and represent angina pectoris. A high index of suspicion is required because the fussiness might be falsely interpreted as infantile colic or reflux. Congestive heart failure often is precipitated by a viral respiratory infection that further increases myocardial oxygen demand. Wheezing may masquerade as bronchiolitis. Examination demonstrates a gallop rhythm or holosystolic murmur

(due to mitral regurgitation). Rarely, the symptoms are not apparent until late childhood or adolescence or even adulthood if there are abundant intercoronary anastomoses.<sup>3,4</sup> On examination, this group of patients may have continuous murmurs. They present with exercise-induced chest pain, syncope, or sudden death.

### ***Laboratory Findings***

Chest radiography shows cardiomegaly. Electrocardiographic findings are consistent with lateral wall myocardial ischemia and include deep Q waves in lead I, aVL, and V4 through V6. Left ventricular leads (V4 to V6) may exhibit ST segment elevation and inverted T waves. Two-dimensional echocardiography may suggest the diagnosis, but Doppler color flow mapping improves the diagnostic accuracy and may demonstrate retrograde flow in the left coronary artery. Abnormal echogenicity of left ventricular papillary muscles may be an additional finding. Abnormal dilation of the proximal right coronary artery is a marker for extensive collateral circulation. Cardiac catheterization with coronary angiography is the gold standard for diagnosis but is necessary only when the diagnosis is ambiguous.

### ***Management***

Surgical revascularization is the definitive treatment. It consists of removal of the LCA from the PA and reimplantation into the aorta. Ligation of the anomalous LCA at its origin from the PA or creation of an intrapulmonary artery baffle from the aortic root to the LCA (Takeuchi procedure) that were performed historically have been abandoned.<sup>5</sup>

Without surgical intervention, mortality is more than 90% in infancy. Patients who survive beyond infancy usually have extensive intercoronary arterial anastomoses. Cardiac transplantation may be considered for infants who have significant myocardial infarction.

Long-term prognosis is variable and depends upon the degree of myocardial infarction sustained before surgical intervention.

## Lessons for the Clinician

Anomalous origin of the left coronary artery from the pulmonary artery is one of the important causes of dilated cardiomyopathy in infants. The symptoms include poor feeding, pallor, and paroxysms of crying, irritability, or diaphoresis and represent angina pectoris. The age of presentation may vary. A high index of suspicion is required because it may mimic infantile colic, gastroesophageal reflux, or viral bronchiolitis. Electrocardiography shows features of myocardial ischemia. Two-dimensional echocardiography may suggest the diagnosis, but Doppler color flow mapping improves the diagnostic accuracy. Surgical revascularization is the definitive treatment.

Kamakshya P. Patra, MD, Robert D. Jackson, MD, Ernest Kiel, MD, Department of Pediatrics, Louisiana State University Health Sciences Center, Shreveport, LA

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## COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER

Since publication of this case (2010), newer modalities for the diagnosis of ALCAPA have been explored. Cardiac computed tomography is a valuable, fast, noninvasive approach to diagnosis of ALCAPA in neonates and can identify variations of vessel anatomy.<sup>1</sup> Cardiac magnetic resonance imaging is used in adult diagnosis but is not currently applicable to neonates because of rapid heart rates affecting imaging, low spatial resolution, requirement for anesthesia, and long study times.<sup>2</sup>

1. Duan X, Yu T, Wang F, et al. Anomalous origin of the left coronary artery from the pulmonary artery in infants: Imaging findings and clinical implications of cardiac computed tomography. *J Comput Assist Tomogr*. 2015;39(2):189–195
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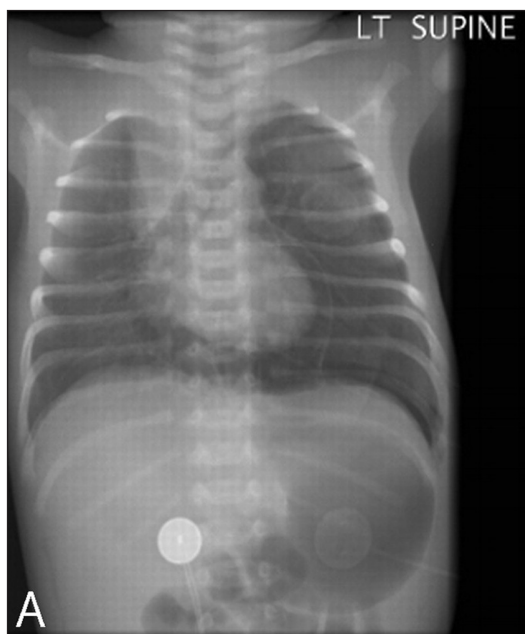
## Newborn With Inaudible Heart Sounds

### Presentation

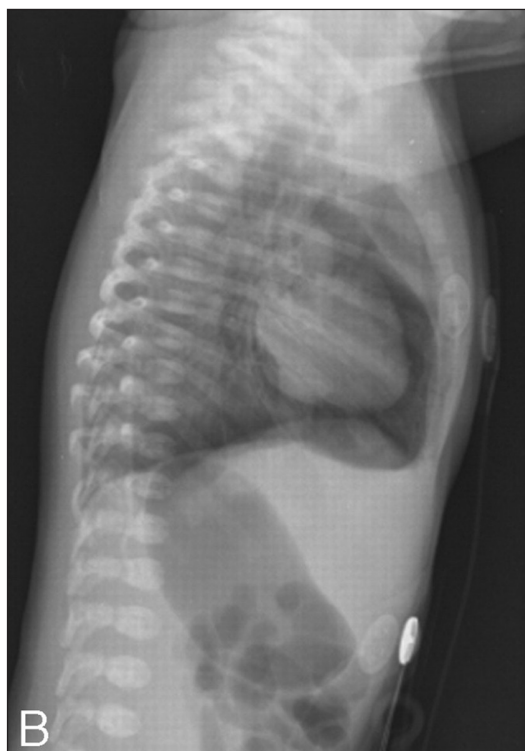
A 2,216-g baby boy is born at 37 weeks' gestation to a 34-year-old gravida 2, para 1 woman. The pregnancy was uncomplicated until the day prior to delivery, when a biophysical profile score of 4/8 was obtained on assessment. Fetal heart rate decelerations to 80 beats/min and multiple late decelerations are noted the evening of delivery, and an emergent cesarean section is planned. The male infant is delivered precipitously prior to entering the operating room. Placental abruption is evident after delivery. At birth, the baby is limp but has spontaneous respirations, with a respiratory rate of 60 breaths/min. Mild intercostal retractions are evident. Femoral pulses are weak, but the heart rate is detected at 130 beats/min. On auscultation, heart sounds are not audible. Apgar scores are 7, 7, and 8 at 1, 5, and 10 minutes, respectively.

Shortly after initial assessment, continuous positive airway pressure (CPAP) is applied at 4 to 5 cm H<sub>2</sub>O, and the baby is transported to the neonatal intensive care unit, where the blood pressure is 44/16 mm Hg (mean, 27 mm Hg) and the oxygen saturation is 98% (with CPAP). Color and tone are poor, and the baby subsequently receives bag-and-mask ventilation and a bolus of 10 mL/kg normal saline via a peripheral intravenous infusion. Color and perfusion do not improve with these interventions. Chest radiography is obtained at 1 hour after delivery, and electrocardiography shows low voltages in all leads. Umbilical venous and arterial lines are inserted, and the baby is intubated with a 3.0 endotracheal tube after receiving atropine, morphine, and succinylcholine. Mechanical ventilation is initiated on initial settings of rate, 40 breaths/min; inspiratory pressure, 12 cm H<sub>2</sub>O; expiratory pressure, 4 cm H<sub>2</sub>O; and FiO<sub>2</sub>, 0.6. A dopamine infusion is started, running at a rate of 10 mcg/kg per minute. Blood pressure and perfusion show minimal improvement despite inotropic support. Arterial cord pH is 7.15, and initial blood counts show white blood cell count,  $15.5 \times 10^3/\text{mCL}$  ( $15.5 \times 10^9/\text{L}$ ); hemoglobin, 14.9 g/dL (149 g/L); and platelets,  $131 \times 10^3/\text{mCL}$  ( $131 \times 10^9/\text{L}$ ). Arterial blood gas measurements obtained after intubation show pH, 7.32; PCO<sub>2</sub>, 36 mm Hg; PaO<sub>2</sub>, 64 mm Hg; HCO<sub>3</sub>, 18 mmol/L. A chest radiograph is shown in Figure 2.1.





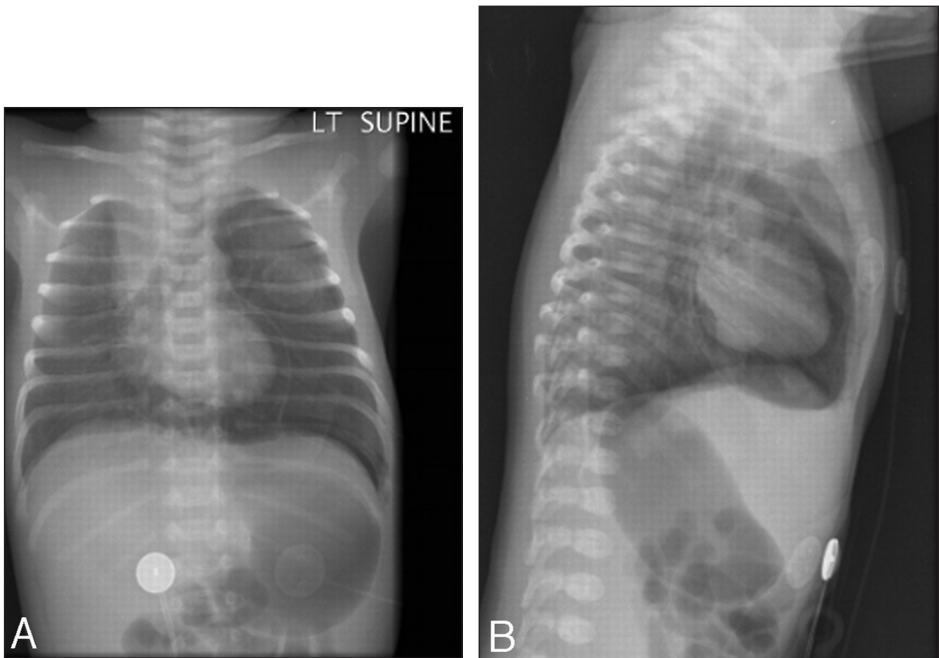
**Figure 2.1.** Anteroposterior chest radiograph and lateral chest view.



*Take a moment to consider the diagnosis in this infant.*

## Discussion

Shock in a newborn has a relatively wide differential diagnosis, including hypovolemic shock (eg, placental abruption), septic shock (eg, group B streptococcal infection), and even cardiogenic shock from asphyxia or congenital heart disease. This case is unique in its clinical presentation because the heart sounds were not audible at birth, electrocardiographic voltages were low, and the neonate's perfusion showed minimal response to fluids or dopamine. The initial radiograph obtained at 1 hour after delivery (Figure 2.2) revealed a spontaneous pneumopericardium (PPC) from birth.



**Figure 2.2.** A. Anteroposterior chest radiograph obtained 1 hour after delivery demonstrates pneumopericardium. The halo sign, a pericardial line, and infracardiac air are visible. B. The lateral view clearly demonstrates the halo of air surrounding the heart.

## ***Cause and Pathogenesis***

The exact cause of PPC remains unknown, but many authors have speculated that interstitial pulmonary air dissects into the mediastinum, entering the pericardial space at the reflection of the pericardial membrane and the pulmonary vessels. In a retrospective review of 50 neonates who had PPC, the most common risk factors were prematurity, low birthweight, presence of respiratory distress syndrome, and the requirement for mechanical ventilation. Other contributory factors were a history of cardiopulmonary resuscitation with intracardiac drug administration and improper endotracheal tube placement. There have been several case reports of neonatal PPC in the absence of mechanical ventilation, usually associated with significant lung disease or the provision of continuous positive airway pressure prior to clinical deterioration. However, spontaneous PPC from birth also has been reported, presenting with an absence of heart sounds and poor perfusion in the delivery room.

## ***Clinical Presentation***

This patient had a typical clinical presentation for PPC. Cyanosis, muffled heart sounds, hypotension, and poor capillary refill are the key components to quick diagnosis. Bradycardia also has been noted in 52% of affected neonates. Cardiac tamponade and cardiac arrest represent one severe end of the spectrum of illness caused by PPC. On the other end of the spectrum are patients who remain asymptomatic and never progress to the development of cardiac tamponade despite radiographic confirmation of the diagnosis. In fact, this was described as early as 1974 in a case series published by Varano: “Although the radiograph suggested the presence of significant amounts of pericardial air, no tamponade was apparent (blood pressure remained constant), and spontaneous resolution of the pneumopericardium occurred.”<sup>1</sup>

## ***Radiographic Features***

The radiographic appearance of PPC has been described best as the classic “halo” sign: a continuous radiolucent band of air conforming to the shape of the heart. In some cases a pericardial line also may be detected, extending inferolaterally from the pericardial reflection at the great vessels. At times, it may be difficult to distinguish PPC from other forms of air leak, such as a pneumomediastinum or a pneumothorax. These conditions may be differentiated by noting that air in the pericardial space may extend inferior to the heart, with air in the mediastinum or pleural cavity typically not present.

## ***Management***

The management of PPC is dictated by the clinical presentation of the patient. Asymptomatic infants usually do not require direct intervention. Those who have signs of cardiac tamponade need immediate treatment with pericardial

decompression (Figure 2.3). Emery and associates have reported recurrences of PPC in 100% of newborns who had severe respiratory disease, leading to the suggestion that placement of an intrapericardial suction catheter is prudent for successful management.<sup>2</sup> However, pericardial drainage catheters have been complicated by hemopericardium, resulting in death by tamponade.<sup>3</sup> Thus, pericardial drainage tubes probably should be reserved for infants in whom PPC with tamponade recurs, where a drainage tube potentially could be lifesaving.



**Figure 2.3.** Chest radiograph obtained after needle pericardiocentesis demonstrates resolution of pneumopericardium.

### ***Lessons for the Clinician***

Pneumopericardium should be considered in the differential diagnosis of a newborn in shock, particularly those in whom heart sounds are absent and who do not show clinical improvement with fluid resuscitation. A clinical diagnosis can be made rapidly by demonstration of a classic halo sign on chest radiography. Treatment via pericardiocentesis to evacuate pericardial air is indicated in infants who demonstrate cardiovascular instability.

*Adam Cheng, MD, Anthony Iacolucci, RRT, Hilary Whyte, MD, The Hospital for Sick Children, Toronto, Ontario, Canada*

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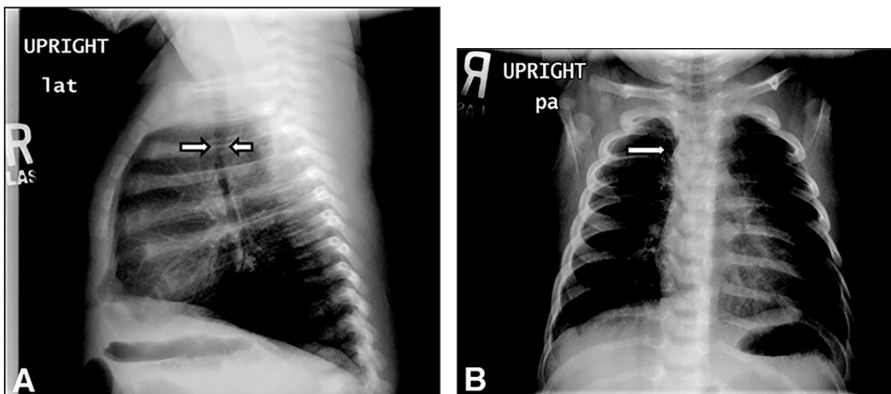
For those seeking additional expertise on performing a pericardiocentesis, refer to the video and step-by-step procedure guidelines in Ruoss JL, Smith-Raska M, Doherty EG. Emergent pericardiocentesis. *NeoReviews*. 2016;17:e627-e629. View the video at <http://neoreviews.aappublications.org/content/17/10/e627>.

## Noisy Breathing Since Birth

### Presentation

A 4-week-old male neonate presents to the clinic with a history of “noisy breathing since birth.” His mother reports that the noise is unaffected by crying, feeding, agitation, or position. She denies any history of fever, cyanosis, vomiting, choking, diaphoresis, murmur, or seizures. The infant was born at term, weighing 3,600 g, to a primigravid mother via normal vaginal delivery, and there were no perinatal complications. There are no findings of note on family history. The child is gaining weight satisfactorily on formula feedings.

On physical examination, the well-nourished infant appears in no apparent distress. His temperature is 37.0°C, heart rate is 127 beats/min, respiratory rate is 36 breaths/min, and blood pressure is 66/44 mm Hg. Oxygen saturation is 96% on room air. Capillary refill time is 2 seconds, with good peripheral pulses and warm extremities. There is no obvious facial dysmorphism or cutaneous hemangioma. Coarse inspiratory stridor is apparent, and chest auscultation reveals coarse breath sounds in all areas. The rest of the physical findings are normal. Chest radiography provides hints about the cause of stridor (Figure 3.1). Additional evaluation confirms the diagnosis.



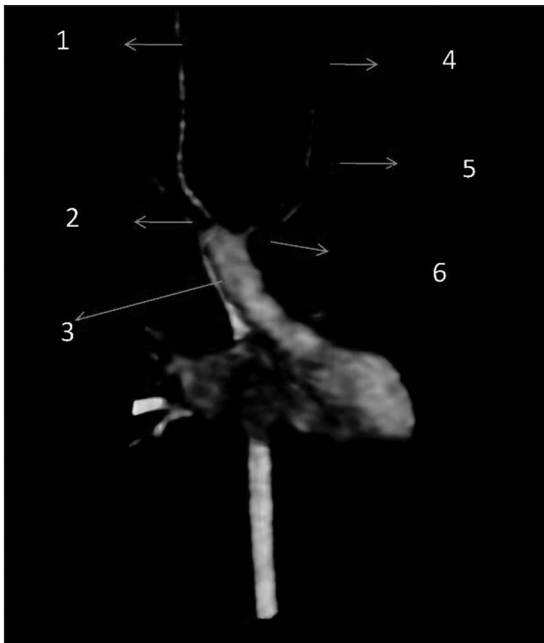
**Figure 3.1.** A. Lateral chest radiograph. B. Anteroposterior view.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

Chest radiography revealed a right-sided aortic arch and indentation of the trachea at the level of the arch (Figure 3.1). The cardiac silhouette appeared normal and the lung fields were clear. Because a vascular abnormality was suspected, magnetic resonance angiography of the chest was performed, and it demonstrated a right-sided aortic arch with mirror-image branching (Figure 3.2). A diverticulum of Kommerell was apparent, with narrowing of the trachea at the level of the arch to the level of the proximal mainstem bronchi (Figure 3.3). The narrow portion measured approximately 40% compared with the proximal trachea at the level of thoracic inlet. Echocardiography revealed the same vascular anomaly with a structurally normal heart. Laryngoscopy ruled out any abnormalities of vocal cords.

Elective surgery was undertaken at 4 months of age. The vascular ring was addressed by division and resection of ligamentum arteriosum via left thoracotomy. The post-operative course was uneventful, except for chylothorax, which was drained.



**Figure 3.2.** Magnetic resonance angiography (front view) showing right-sided aortic arch (3), innominate artery, the first branch from the arch (6) arising from the left side of the arch and giving rise to left carotid artery (4) and left subclavian artery (5). Also seen are the right carotid artery (1) and right subclavian artery (2) arising separately from the arch.



**Figure 3.3.** Magnetic resonance angiography (back view) showing right-sided aortic arch and diverticulum of Kommerell (a), which forms part of the vascular ring.

### ***Differential Diagnosis***

Stridor in an infant can have numerous causes. It could be due to laryngeal obstruction (eg, laryngomalacia, papilloma, laryngeal webs, foreign body, vocal cord paralysis), tracheobronchial obstruction (eg, tracheomalacia, subglottic stenosis, subglottic hemangiomas), infections (eg, croup, tracheitis, epiglottitis), extrinsic masses (eg, thyroid enlargement, mediastinal mass, vascular ring, lobar emphysema), hypocalcemia, or neurogenic anomalies (eg, Chiari crisis).<sup>1</sup>

### ***The Condition***

Vascular rings are aortic arch anomalies that surround the trachea and esophagus, forming a complete or partial ring. They include double aortic arch, right aortic arch (RAA), persistent fifth aortic arch, interrupted aortic arch, cervical aortic arch, and anomalous origin of left pulmonary artery from the right pulmonary artery (pulmonary sling). Their incidence is less than 1% of all cardiovascular malformations. They can present as stridor, choking cough, or dysphagia and can masquerade as asthma.<sup>2,3</sup>

Embryologically, the aortic arch is formed by the 6 paired branchial arches (I through VI) connecting the truncus aorticus of the embryonic heart tube and the paired dorsal aortae (which subsequently fuse to form the descending aorta). The right or left aortic arches correspond to the bronchus over which they cross. The arches are derived from branchial pouches by cellular differentiation and regress by selective apoptosis. Both right- and left-sided ductus arteriosus are found



early in development. Normally, the right ductus arteriosus regresses and the right arch is interrupted beyond the right subclavian artery. The innominate artery, arising from the proximal remnant portion of the right aortic arch, gives rise to the right carotid and right subclavian arteries. The left aortic arch (LAA) gives rise to the left carotid and left subclavian arteries. Chromosome 22q11 microdeletion frequently is associated with aortic arch anomalies. Perturbation of migration of neural crest cells is believed to be the underlying mechanism.<sup>4</sup>

Right aortic arches are of four major types: with “mirror-image branching” of brachiocephalic vessels, with an aberrant left subclavian artery, with retroesophageal diverticulum, and with left descending aorta. The first type almost always is associated with cyanotic heart disease, with a predilection for tetralogy of Fallot and truncus arteriosus. This infant was unusual because despite having an RAA with mirror-image branching, he did not have any intracardiac lesion. Very few cases of RAA with mirror-image branching and no underlying intracardiac defect have been reported.<sup>5</sup> The RAA with mirror imaging results if the right fourth branchial arch persists and the LAA beyond the left subclavian artery dissolves. The left dorsal aorta persists as the retroesophageal diverticulum of Kommerell, which is connected to the left seventh intersegmental artery that forms the left subclavian artery. The first branch from the arch is an innominate artery, representing the proximal portion of the LAA. The innominate artery gives rise to left subclavian and left carotid arteries. The aortic arch subsequently passes to the right and gives rise to the right carotid and right subclavian arteries. The vascular ring is completed by the ductus arteriosus or ligamentum arteriosum, which connects the descending aorta to the left pulmonary artery.<sup>6</sup>

In a child who has stridor, this anomaly should be suspected when there is an RAA on a chest radiograph. Magnetic resonance angiography is diagnostic, and management consists of surgical ligation of the ligamentum arteriosum. Chest radiography also can provide clues about other arch anomalies. For example, double aortic arch demonstrates indentation of the air column on the right side superiorly by the RAA and inferiorly on the left side by the LAA. In the case of pulmonary sling, a lateral chest radiograph reveals a soft-tissue space in between the trachea and esophagus at the level of carina. It is the only arch anomaly that demonstrates an anterior indentation on the esophagus with barium esophagography.<sup>6</sup>

### **Lessons for the Clinician**

Vascular ring should be considered in the differential diagnosis of stridor in a neonate. A chest film can suggest the diagnosis of vascular ring. Magnetic resonance angiography is the gold standard for the diagnosis of arch anomalies.

*Kamakshya P. Patra, MD, Louisiana State University, Shreveport, LA*

*Himeshkumar Vyas, MD, William R. Morrow, MD, Arkansas Children's Hospital, Little Rock, AR*

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## Fetal Bradycardia That Persists Postnatally

A male infant is born at 39 2/7 weeks' gestation to a 41-year-old G5P2022 woman who had negative findings on prenatal laboratory tests and group B Streptococcus testing. His Apgar scores are 8 and 9 at 1 and 5 minutes, respectively, with points being subtracted for color. He requires no resuscitation. On the first postnatal day, his heart rate decreases to less than 80 beats/min while awake. Clinically, he appears fine and has no cyanosis or respiratory distress.

Findings on physical examination include a temperature of 98.4°F (36.9°C), heart rate of 92 beats/min, respiratory rate of 35 breaths/min, blood pressure of 69/30 mm Hg, and pulse oximetry of 100% on room air. There are no retractions, flaring, or grunting, and breath sounds are equal bilaterally. Cardiac examination reveals regular rate and rhythm, a I/VI systolic murmur throughout the precordium that is loudest at the left lower sternal border, and femoral and brachial pulses that are +2 bilaterally. Tone is normal, and the anterior fontanelle is open and soft.

Further history reveals that the baby had fetal bradycardia in utero with appropriate variability. The mother had been screened for rheumatologic conditions, specifically systemic lupus erythematosus, and test results were negative. Results of fetal echocardiography at 32 weeks' gestation reportedly were normal. Echocardiography and electrocardiography performed on the baby reveal the diagnosis (Figure 4.1).

*Take a moment to consider the diagnosis in this infant.*

### Discussion

Echocardiography revealed mild dilatation of the right and left ventricles and multiple small, posterior, muscular ventricular septal defects with a small left-to-right shunt.

Electrocardiography documented bradycardia (about 60 beats/min) and what appeared to be either complete or a Mobitz type II heart block (Figure 4.1). However, there also was a significantly prolonged QT interval.

These findings led to the diagnosis of prolonged QT syndrome with pseudo 2:1 heart block. Because the QT interval was significantly prolonged, the ventricle



**Figure 4.1.** Electrocardiography on the first postnatal day.

continued to depolarize when the next atrial impulse reached the ventricle, resulting in only every second atrial impulse being conducted to the ventricle and leading to the picture of bradycardia with pseudo heart block.

### ***Differential Diagnosis***

This baby presented with fetal bradycardia as the only sign of a potentially fatal condition. Although prolonged QT syndrome is one of the conditions known to cause fetal bradycardia, the most common causes of bradycardia are physiologic sinus rhythm or heart block. Heart block usually is diagnosed in utero by M-mode echocardiography, which shows complete dissociation of the atrial and ventricular rates, with no consistent relationship to ventricular contractions.

Two-dimensional echocardiography needs to be performed when bradycardia occurs to look for cardiac anomalies, which are seen in 40% to 60% of affected fetuses. Echocardiography also helps to evaluate for fetal hydrops, which occurs if there are anomalies, but is rare in isolated cases of heart block. Some common anomalies causing heart block are left atrial isomerism, atrioventricular septal defect, and transposition of the great arteries. Myocarditis also may cause bradycardia, especially when it is associated with congenital lupus erythematosus. In this condition, maternal antibodies induce fetal myocarditis, with destruction of the conducting fibers, although otherwise the heart is structurally normal.

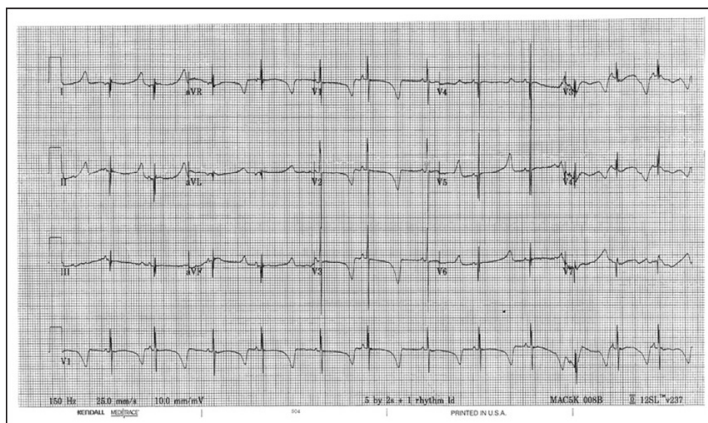
Short episodes of sinus bradycardia are common and physiologic in the fetus due to transient fetal head or umbilical cord compression, but new-onset sinus bradycardia is considered nonreassuring and can result in hypoxic death. Maternal hypotension; maternal seizures; paraventricular block anesthesia; and impaired fetal oxygenation from placental abruption, uterine rupture, or prolapsed umbilical cord also may cause fetal bradycardia.

## Pathophysiology

In this case, prolonged QT was diagnosed successfully early in life, but in many unfortunate cases, the diagnosis is not made until it is too late. Prolonged QT syndrome is one of the causes associated with sudden unexplained death. Some cases of prolonged QT are diagnosed after symptoms of syncope, whether related to exercise or medication induced, or after unexplained seizures. From a molecular standpoint, prolonged QT is caused by defects governing ion channels and membrane proteins. More than 50 genetic mutations in 4 critical cardiac ion channels have been demonstrated in inherited prolonged QT syndrome.<sup>1</sup> A particular inherited form, termed Jervell and Lange-Nielson syndrome, has an autosomal recessive inheritance pattern and is associated with congenital hearing loss. Thus, patients diagnosed with prolonged QT syndrome must undergo hearing screening.

## Management

Although the infant in this case exhibited bradycardia, beta blocker therapy was initiated. The standard management options for prolonged QT syndrome include beta blockers, implantable pacemaker or defibrillator, and a surgical procedure that involves a left cervicothoracic sympathetic ganglionectomy. We used beta blockers in this patient because we believed that they would delay the impulse being released from the atrioventricular node to the ventricle, thus making the occurrence of a one-to-one conduction more likely. The heart block resolved with therapy, and after 1 week, the QT interval decreased slightly, but remained relatively prolonged (Figure 4.2).



**Figure 4.2.** Electrocardiography tracing documenting slightly decreased QT interval.

The patient was discharged from the hospital on propranolol. The possibility remained that he would receive a pacemaker at an older age.

## Lessons for the Clinician

Pathologic bradycardia occurs infrequently. Although commonly the bradycardia is sinus/physiologic, it can be a warning sign, especially if the heart rate is low when the baby is awake. Electrocardiography is a relatively inexpensive tool that may lead to a lifesaving diagnosis. Prolonged QT syndrome is not common, but its incidence is 3 times that of childhood acute lymphocytic leukemia, and it has long-lasting implications. Interestingly, although the heart rates of affected infants may be initially slow, the best treatment may involve an agent that slows the heart, as dictated by the body's physiology.

*Prashant K. Sura, MD, Medical College of Wisconsin, Milwaukee, WI.*

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### COMMENTARY BY DR JOSEF NEU, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE

In reviewing the literature, I found an interesting article relating antepartum use of selective serotonin reuptake inhibitors (SSRIs) to prolonged QT intervals in both the fetus and neonate. Data were collected on all newborns born at a single tertiary care hospital. Electrocardiograms of infants exposed to SSRIs in utero were compared with those of healthy control newborns matched on gestational age. Fifty-two newborns exposed to SSRIs in the immediate antepartum period were compared to 52 matched control subjects. The mean corrected QT interval was significantly longer in the group of newborns exposed to antidepressants compared with control subjects. All the repolarization abnormalities normalized in subsequent tracings. The authors suggest that this relationship needs to be examined further by using a standardized protocol.<sup>1</sup>

At present the treatment of infants with congenital long QT syndrome is focused on decreasing symptomatic episodes and preventing life-threatening cardiac events. Recent genetic advances in identifying the clinical impact of different types of mutations offer the possibility of developing a patient-specific approach based on genetic diagnosis.

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*Part 2*

# **Dermatology**



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## **Skin Rash, Poor Feeding, and Diarrhea in a 22-Day-Old Boy**

### **Presentation**

A 22-day-old term newborn boy, who was born via normal spontaneous vaginal delivery to a 29-year-old G3P2A0 healthy mother and whose birthweight was 3,700 g, presents to the emergency department because of rash, poor feeding, diarrhea, and irritability. Antenatal serologic testing was negative for syphilis and hepatitis B surface antigen and immune to rubella and toxoplasmosis. Group B Streptococcus screening results are unknown. There were no complications during delivery, and Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The infant has been breastfeeding since birth but was stopped 5 days ago because the mother developed bilateral mastitis and she was started on amoxicillin-clavulanic acid. The infant has been fed with regular formula since that time.

The infant's illness started 3 days ago with frequent (>7 times) watery nonbloody stools, progressive poor feeding, fussiness, and diaper rash. The mother, without medical advice, gave her baby an herbal supplement (anise), and she decided to prepare the formula by adding 80 mL water in place of 60 mL for each scoop of milk powder (diluted formula). She believed that these measures would improve her baby's appetite and compensate for the water loss. Today the baby became lethargic and very irritable, and his diaper rash extended to cover the lower limbs and the abdomen. The mother applied zinc oxide cream to the rash many times. On admission, the infant exhibits right hemibody tonic-clonic movements with his eyes rolling upward, and the admitting physician administers diazepam twice to stop the convulsions.

On physical examination, the ill-looking, lethargic infant has a respiratory rate of 65 breaths/min, heart rate of 170 beats/min, temperature of 36.5°C, blood pressure of 50/30 mm Hg, and transcutaneous oxygen saturation of 95% on room air. He has normal fontanelles, cracked lips, strawberry tongue, and dry mouth. He has normal fast heart sounds, no audible murmur, adequate air entry bilaterally, mild subcostal

retractions, and a soft and moderately distended abdomen with no organomegaly. He has poor suck, weak grasp, and incomplete Moro reflex. He exhibits very red confluent patches over both lower limbs and the abdomen, with clearly demarcated borders, painful and edematous skin in the affected areas, and moderate scrotal edema (Figure 5.1). The rash spares the feet. Vesicles, bullae, purpura, and crusts are not present. Yellowish secretions are noted over the umbilicus, although the cord stump fell off 10 days before presentation.



**Figure 5.1.** Red confluent patches over both lower limbs and the abdomen, with clearly demarcated borders, edematous skin in the affected areas, and moderate scrotal edema.

The clinician administers an urgent bolus of normal saline and supplemental oxygen. A complete sepsis evaluation is undertaken, including cerebrospinal fluid (CSF) analysis and culture, stool analysis and culture, and umbilical swab culture. In addition, intravenous cefotaxime, vancomycin, and acyclovir are administered with dopamine 10 mcg/kg per minute and phenobarbital.

Blood tests that include electrolytes, blood glucose, creatinine, blood urea nitrogen, calcium, phosphorus, magnesium, and liver function are ordered. Laboratory results yield a white blood cell (WBC) count of  $2.9 \times 10^3/\text{mcL}$  ( $2.9 \times 10^9/\text{L}$ ) with 45% segmented forms and 47% lymphocytes, C-reactive protein of 180 mg/L (18 mg/dL) (normal,  $<5 \text{ mg/L}$  [ $<0.5 \text{ mg/dL}$ ]), and sodium of 109 mEq/L (109 mmol/L). The other laboratory results are within normal ranges, including platelet count, prothrombin time (PT), and partial thromboplastin time (PTT). An intravenous bolus of hypertonic saline 3% is administered to correct the symptomatic hyponatremia.

The infant is admitted to the neonatal intensive care unit (NICU), where the rash worsens dramatically and characteristically over the next hours. One test helps to determine the diagnosis.

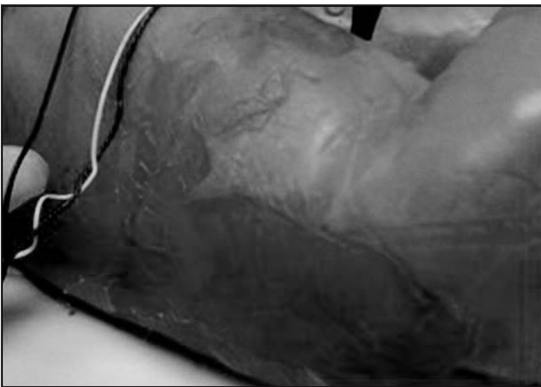
*Take a moment to consider the diagnosis in this infant.*

## Discussion

A few hours after admission to the NICU, the baby became hemodynamically stable on supplemental oxygen and intravenous perfusion. Purpuric skin lesions were evident over the legs, with two large bullae over the lateral aspects of both legs and black necrotic lesions in the base of bullae and around them (Figure 5.2). These lesions are compatible with necrotizing fasciitis. The rash extended to involve the thorax up to the nipple line. Three days after admission, extensive skin desquamation occurred over the affected areas (Figure 5.3) as well as the hands and feet.



**Figure 5.2.** Large bulla over the lateral aspect of the leg, with black necrotic lesions in the base and surrounding the bulla.



**Figure 5.3.** Extensive skin desquamation that developed 3 days after admission.

At this time, blood and umbilical swab cultures grew group A *Streptococcus* (GAS) sensitive to penicillin, cefotaxime, and vancomycin. The other cultures, including CSF, were negative. Clinically, the baby was stable but remained irritable. Laboratory tests obtained on the third day of hospitalization revealed WBC count,  $18 \times 10^3/\text{mcL}$  ( $18 \times 10^9/\text{L}$ ) with 80% segmented forms and 17% lymphocytes; platelet count,  $7 \times 10^3/\text{mcL}$  ( $7 \times 10^9/\text{L}$ ); PT, 20 sec (normal, 11.9 sec); and PTT, 84 sec (normal, 30.4 sec). Vitamin K, platelets, and fresh frozen plasma transfusion were administered twice as part of treatment for disseminated intravascular coagulation (DIC). Blood tests revealed albumin within normal range, high D-dimer, and low fibrinogen.

The findings of GAS in blood culture with hypotension, characteristic rash, and DIC confirmed the diagnosis of streptococcal toxic shock syndrome (STSS), even though the findings were serial and not simultaneous. Over the next 2 days, platelet counts, PT, and PTT normalized.

Multiple skin nodules appeared scattered throughout the desquamated skin at day 8 of hospitalization (Figure 5.4). They were drained surgically and yielded pus that grew *S epidermidis* sensitive to vancomycin. The necrotic lesions over the legs were debrided, and surgical findings confirmed the presence of necrotizing fasciitis. Despite appropriate therapy, new diffuse abscesses continued to appear but always were limited to the areas previously affected by the initial cellulitis. To rule out immunodeficiency, a complete immunologic profile that included immune globulin dose and peripheral blood flow cytometry was performed and yielded normal results. Skin biopsy also demonstrated no abnormalities.



**Figure 5.4.** Skin nodules in the desquamated skin at day 8 of hospitalization.

The baby was discharged from the hospital after 7 weeks of treatment, and no new abscesses appeared over the last week of hospitalization. Three weeks after discharge, the 3-month-old baby is healthy, thriving, and without new skin lesions, although the scars of old abscesses and necrotizing fasciitis are obvious (Figure 5.5). The abscesses most likely were due to superinfection after breakdown of normal skin barriers due to the severe cellulitis and desquamation. The parents were

encouraged to continue close follow-up monitoring and to repeat the dose of immunoglobulin E after 6 months of age to rule out hyper-IgE syndrome (Job syndrome), a known cause of recurrent skin abscesses.



**Figure 5.5.** Scars of old abscesses and necrotizing fasciitis.

### ***The Condition***

Group A *Streptococcus* causes the broadest spectrum of clinical syndromes of any bacteria, varying from mild infections such as mild skin infection and omphalitis to invasive, life-threatening infections such as STSS and meningitis. The incidence of invasive GAS infection is highest in infants and older people. In neonates, infection can result from intrapartum transmission, especially in early-onset infection up to 5 days of age, or from contact transmission in both early- and late-onset types, with the primary focus of infection being omphalitis and cellulitis. The source of infection generally is not identified in late-onset infection.

Group A *Streptococcus* had been recognized as a major causative agent of neonatal sepsis before the antibiotic era and subsequently almost disappeared.<sup>1</sup> However, an increase in the incidence of invasive infections caused by GAS has been noted

since 1980. After an extensive review of the literature published since 1966 using the entire database available online, we found only 42 cases of invasive neonatal GAS, including 2 nursery outbreaks, and almost all cases were in the past 20 years.<sup>1,2,3,4</sup>

M protein, encoded by the *emm* gene, is an important virulence factor in the pathogenesis of GAS infections. *Emm* types 1 and 3 were reported to be more frequently encountered in invasive infections in both neonates and adults.<sup>3,5</sup>

Data on GAS prophylaxis for either neonatal or maternal disease prevention are limited. Results of population-based surveillance for postpartum GAS disease suggested that maternal postpartum disease might be preventable.<sup>3</sup> Prenatal GAS screening is more controversial because of the low rate of vaginal-rectal carriage in late pregnancy. More studies are needed to assess the importance of maternal GAS screening during pregnancy and prophylactic perinatal treatment.

### ***Clinical and Paraclinical Manifestations***

The major clinical expressions of early-onset invasive disease are pneumonia or empyema, soft-tissue infection, and STSS. Common characteristics of early-onset disease include respiratory distress, rapid deterioration, and a high mortality rate, regardless of the focus of infection. Nearly 25% of neonates had an exanthema on presentation. A lack of fever is common. Approximately one third of neonates in the early-onset group were delivered preterm, which may, in part, have been the result of GAS-associated chorioamnionitis. The fulminant nature and concurrent maternal factors indicate that early-onset GAS disease may be a manifestation of hematogenous dissemination or a toxin-mediated syndrome with an in utero onset.

The major clinical expression of late-onset disease is soft-tissue infections and meningitis; pneumonia and STSS are less common. Rash is also seen in a significant percentage of patients. In contrast to early-onset infection, fever is a common presenting sign in late-onset sepsis.

Streptococcal toxic shock syndrome is often accompanied by focal infection such as cellulitis or necrotizing fasciitis. Streptococcal toxic shock syndrome plus necrotizing fasciitis are associated with a high mortality rate. Defining characteristics of classic STSS include hypotension or shock plus at least 2 of the following 6 criteria occurring concurrently or serially: scarlatiniform rash, hepatic abnormalities, renal abnormalities, DIC, respiratory distress syndrome, or extensive soft-tissue necrosis (necrotizing fasciitis). These disorders must occur in the absence of other explanations or other positive bacterial cultures.

Group A *Streptococcus* omphalitis is a potentially invasive infection if not adequately treated at early stages. The umbilical stump is colonized while the infant is in the nursery. Similar to staphylococcal infections, clinical manifestations may be

few or absent while the infant is still in the nursery. Most often, a colonized infant develops chronic, oozing omphalitis days later. Colonization of the umbilical cord by GAS may persist for up to 8 weeks after birth.

Leukocytosis is common in both early- and late-onset infections, but leukopenia is almost exclusively seen in the early-onset type of infection, unlike in this case. C-reactive protein is high in most cases. In suspected invasive GAS infection, complete sepsis evaluation must be performed, including cultures of blood, CSF, and any suspected focal site. In necrotizing fasciitis, imaging studies often delay, rather than facilitate, the diagnosis. Clinical suspicion of necrotizing fasciitis should prompt surgical inspection of the deep tissues, with Gram stain and culture of surgical specimens.

## **Treatment**

Group A *Streptococcus* is sensitive to a variety of antibiotics administered either alone or in combination. Penicillin is the most commonly prescribed antibiotic for GAS invasive infection in children. Combination treatment with a beta-lactam agent and clindamycin may improve the outcome, especially in STSS.<sup>6</sup> Other antibiotics used include aminoglycosides, second- and third-generation cephalosporins, and vancomycin. Accessible sites of infection should be aggressively drained and irrigated as soon as possible. If necrotizing fasciitis is suspected, immediate surgical exploration or biopsy is crucial to identify deep soft-tissue infection that should be debrided immediately. To decrease the risk of superinfection, skin care of the affected site with local antiseptic is important, especially after desquamation. In addition, all supportive measures should be considered, including fluids, inotropic agents, and blood products.

## **Lessons for the Clinician**

The increasing incidence of invasive GAS in all age groups, including neonates, should prompt clinicians to consider GAS as an offending agent in neonatal sepsis, especially in the presence of any maternal perinatal GAS infection and if the newborn presents with initial skin lesions or omphalitis. Prompt and appropriate treatment may reduce complications and mortality. Omphalitis and cellulitis must always be treated early and appropriately. To decrease the risk of superinfection, skin care of the affected site with local antiseptic is crucial, especially after desquamation.

*Mossaab Hassoun, MD, Mohamad Fares, MD, Mariana El-Hajj, MD, Hassan Fakhoury, MD, Imad Chokr, MD, Pediatrics Department, Rafic Hariri University Hospital, Beirut, Lebanon, affiliated with the American University of Beirut and Lebanese University, Lebanon*



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## A Rash After Intensive Phototherapy

### Presentation

A 2.9-kg female infant is born at 35 weeks' gestation to a 33-year-old G4P3 woman via cesarean section due to chronic hypertension complicated by superimposed preeclampsia. The mother's blood type is A-negative; the antibody screen is positive for anti-D, anti-C, and anti-G antibodies; she has no prior history of sensitization; and her serologies are negative. The Apgar scores are 7 and 9 at 1 and 5 minutes, respectively.

At birth, the infant appears pale and exhibits tachycardia, moderate hepatosplenomegaly, tachypnea, and mild respiratory distress requiring supplemental oxygen. Complete blood count and blood cultures are obtained, and ampicillin and gentamicin are started. The admission hematocrit is 21% (0.21), with a reticulocyte count of 64%. An umbilical venous catheter is placed for intravenous (IV) access. The infant receives a transfusion of packed red blood cells for significant anemia associated with tachycardia.

Prophylactic phototherapy is started because of Rh sensitization. The cord blood bilirubin measures 11.4 mg/dL (195 mc mol/L). The infant's blood type is A-negative, and the antibody screen is positive for anti-D and anti-C antibodies, with a positive direct Coombs test. The red blood cell phenotype reveals the presence of "C" antigen. This is a very uncommon antigen in an Rh-negative infant, but the antigen had stimulated the anti-C antibodies that traversed the placenta and caused severe hemolysis of the newborn. At 7 hours of age, the infant's bilirubin is 16 mg/dL (273.6 mc mol/L). She is given two doses of IV immune globulin, and phototherapy is intensified.

After 24 hours of intensive phototherapy, the infant develops a large reddish-purple discoloration on her abdomen that resembles a severe burn (Figure 6.1). The well-demarcated, erythematous, purpuric rash is present over the areas closely exposed to the phototherapy lights and does not blanch with diascopy. No vesiculobullous eruptions, edema, or tenderness is noted. The unexposed areas (part of the skin covered by the tape used to secure the umbilical venous catheter and

electrocardiography electrodes) are spared. Phototherapy is discontinued, and a double-volume exchange transfusion is performed. Postexchange total serum bilirubin measures 8.1 mg/dL (138.5  $\mu\text{mol/L}$ ). No further exchange transfusion or phototherapy is required.



**Figure 6.1.** Reddish-purple erythematous rash over the areas closely exposed to phototherapy, with sparing of unexposed areas.

The combination of hemolytic anemia, hyperbilirubinemia, and photosensitivity prompt additional laboratory tests before exchange transfusion that reveal the cause of the rash.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

### Diagnosis

The purpuric nature of the photodistributed skin findings suggested a disorder of porphyrin-related metabolism. Plasma and urine porphyrins concentrations were measured before the exchange transfusion. The values were significantly elevated (Table 6.1) and decreased by 2 weeks of age, suggesting transient porphyria. A punch biopsy of the skin showed extravasated erythrocytes in the superficial dermis without significant inflammation or keratinocyte necrosis. This finding is compatible with purpuric phototherapy-induced eruption. The rash began to fade (Figure 6.2) after discontinuation of phototherapy and disappeared by 2 weeks of age. There was no recurrence of the rash at assessment 3 months later.

**Table 6.1. Porphyrin Profile at Postnatal Days 3 and 13**

Laboratory Test	Day 3	Day 13
Plasma:		
Total porphyrin (normal, 0 to 1 mcg/dL)	15.9 mcg/dL	4.7 mcg/dL
Coproporphyrin fraction	8.7 mcg/dL	4.1 mcg/dL
Protoporphyrin fraction	6.9 mcg/dL	0.5 mcg/dL
Urine:		
Uroporphyrins (normal, 0 to 4 mcmol/mol)	25 mcmol/mol	5 mcmol/mol
Hepatocaryoxylate (normal, 0 to 2 mcmol/mol)	22 mcmol/mol	4 mcmol/mol
Coproporphyrin (normal, 0 to 22 mcmol/mol)	229 mcmol/mol	95 mcmol/mol
Stool:		
Coproporphyrin and protoporphyrin	Within normal range	Not assessed



**Figure 6.2.** Gradual fading of the rash, with complete disappearance by 2 weeks of age.

The key to diagnosis was the localization of the rash in phototherapy-exposed areas closest to the phototherapy lamps, sparing of sites protected from phototherapy, absence of blisters, clearing of the eruption with discontinuation of phototherapy, and decreasing porphyrin values. The combination of transiently elevated circulating porphyrin concentrations, phototherapy-induced eruptions, and the absence of inflammation and keratinocyte necrosis in skin biopsy confirmed the diagnosis of purpuric phototherapy-induced eruptions.

The differential diagnosis of photosensitization in a neonate includes a wide range of disorders such as xeroderma pigmentosum, transplacentally transferred collagen vascular disorders such as neonatal lupus, diseases manifesting with blisters such as epidermolysis bullosa, photosensitizing drugs such as furosemide, phototherapy-induced burns, and hereditary porphyrias.

Phototherapy-induced eruptions have been described in transfused neonates.<sup>1,2,3</sup>

This infant received a transfusion prior to the initiation of phototherapy. The exact mechanism for the development of increased porphyrins in phototherapy-induced eruptions is not clear. Proposed mechanisms for the transient elevation in circulating porphyrin include hepatic cholestasis and poor hepatic porphyrin metabolism as well as release of porphyrins by hemolysis of young erythrocyte precursors, including reticulocytes, which contain at least a tenfold higher protoporphyrin concentration than do mature erythrocytes.<sup>4</sup>

The combination of diffuse erythema, blisters, and a painful and tender rash following phototherapy has been reported as phototherapy-induced burns in the past.<sup>5</sup> The use of Plexiglas shield, which is now the standard of care in all neonatal intensive care units, effectively eliminates the ultraviolet A irradiation in the wavelength of the 300 to 400 nm range that is associated with burns. Histopathologic evaluation of the lesional skin biopsy shows epidermal edema and necrotic keratinocytes or inflammatory infiltrates in phototherapy-induced burns.

The porphyrias are a group of diseases characterized by abnormalities of porphyrin-heme metabolism. Each type results from deficient activity of one of the enzymes of the heme biosynthetic pathway, which leads to an accumulation of heme precursors. In infants, the enzyme defects always are inherited. Clinically, the porphyrias can be separated into those manifesting cutaneous photosensitivity, neurovisceral symptoms, or both. Photosensitivity is maximum for ultraviolet wavelengths between 400 and 410 nm (Soret band), the spectrum of maximum absorptions of porphyrins. The erythropoietic type of congenital erythropoietic porphyria and erythropoietic protoporphyria appear at birth or early infancy, when the child is exposed to sunlight, and the hepatic type usually manifests in infancy or later. Serial measurements of plasma, urine, and stool porphyrin should be obtained for definitive diagnosis of hereditary porphyrias. Histologic examination of the lesions may be helpful in differentiating transient porphyrinemia from hereditary porphyrias.

### **Lessons for the Clinician**

Purpuric light eruption should be recognized as a transient, benign, cutaneous eruption in transfused neonates who undergo phototherapy. The characteristic distribution of the eruption in photo-exposed areas and disappearance of the rash with discontinuation of phototherapy is highly suggestive of phototherapy-induced transient porphyrinemia. Serial measurement of plasma, urine, and stool porphyrin as well as histologic examination of the lesion may aid in differentiating transient porphyrinemia from the more serious porphyrias. Management requires a high index of suspicion and discontinuation of exposure to light.

*Jagadish Elumalai, MD, Nirupama Subramanian, MD, Division of Neonatology, University of California, Davis Medical Center, Sacramento, CA.*

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## **Three-Week-Old With Fever and a Desquamating Rash**

### **Presentation**

A 3-week-old white male infant presents to the emergency department for evaluation of extensive facial dermatitis. He was born by vaginal delivery at 39 weeks' gestation to a 27-year-old primigravid woman who had an uncomplicated pregnancy. The maternal prenatal screening results were negative. Apgar scores were 9 at 1, 5, and 10 minutes, and no blisters were noted either at birth or in the immediate perinatal period. His birthweight was 3.6 kg. He is being fed standard cow milk formula and has good weight gain.

Three days ago, he developed perioral redness, which has progressed to involve the entire face. He had been fussy since the onset of the rash but has remained active, has been feeding well, and has had normal urination and stooling. He has had no fevers or other symptoms and is not taking any medications. There is no family history of blistering or other dermatologic disease, and the infant has had no sick contacts.

On physical examination, the infant's weight, height, and head circumference are at the 50th percentile. His temperature is 101.3°F (38.5°C), pulse is 120 beats/min, respiratory rate is 30 breaths/min, and blood pressure is 90/40 mm Hg. Skin examination reveals diffuse erythema, desquamation, fissuring and honey crusting in the perioral and cheek areas (Figure 7.1). Fine desquamation also is apparent in the flexural areas, namely, the axillae (Figure 7.2), groin, and gluteal cleft (Figure 7.3). He has several intact flaccid bullae on the hands (Figure 7.4). He has conjunctival mucus discharge without conjunctival injection but no intraoral lesions. His cardiac, respiratory, abdominal, genitourinary, and neurologic examination results are normal.





**Figure 7.1.** Fissuring and honey crusting in the perioral and cheek areas.



**Figure 7.2.** Desquamation in the axilla.



**Figure 7.3.** Desquamation in the gluteal cleft.



**Figure 7.4.** Erythema and flaccid bullae on the hands and fingers.

Results of laboratory tests include hemoglobin of 14.2 g/dL (142.0 g/L), white blood cell count of  $10.6 \times 10^3/\text{mcL}$  ( $10.6 \times 10^9/\text{L}$ ) (26% neutrophils, 5% bands, 34% lymphocytes, 22% monocytes), and platelet count of  $450.0 \times 10^3/\text{mcL}$  ( $450.0 \times 10^9/\text{L}$ ). Urinalysis findings are normal. Evaluation of the cerebrospinal fluid (CSF) shows 4 white blood cells/mcL, 19 red blood cells/mcL, glucose of 45.0 mg/dL, and protein of 59.0 mg/dL. Gram stain shows no bacteria.

A simple clinical test provides clues to the diagnosis.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

During the lumbar puncture, foci of desquamation were noted on the back at the pressure sites where the physician's nondominant hand was placed while inserting the spinal needle. Similar superficial peeling on the extremities was noted during insertion of a peripheral intravenous line. Such slipping of the superficial skin layers away from the deeper skin layers, known as the Nikolsky sign, along with the other skin findings and lack of mucosal involvement or recent drug use led to the diagnosis of staphylococcal scalded skin syndrome (SSSS).

The differential diagnosis for a febrile infant who has a rash is broad, encompassing serious bacterial infections such as bacterial sepsis and meningitis, herpes simplex virus (HSV) infection, SSSS, toxic epidermal necrolysis, and epidermolysis bullosa. Blood, urine, and CSF cultures were obtained for this infant, and intravenous vancomycin, cefotaxime, and acyclovir were administered. Skin surface cultures for bacteria and virus were obtained for the left axilla, gluteal cleft, and nares. At 24 hours, all skin surface cultures were positive for *Staphylococcus aureus*, and viral cultures were negative. Acyclovir and cefotaxime were discontinued at 48 hours after confirmation of negative bacterial blood and CSF cultures and a negative CSF HSV polymerase chain reaction test. Vancomycin was continued for 7 days. The infant's rash improved markedly, he defervesced, and he was discharged from the hospital 7 days after admission in stable condition for follow-up by his primary care physician.

## The Condition

Staphylococcal scalded skin syndrome is caused by infection with a specific strain of *S aureus* that leads to blistering of the upper layer of the skin following release of a circulating exfoliative toxin. Most cases occur in neonates and children younger than 5 years of age and are believed to be due to the inability of this younger age group of children, whose renal function is not yet mature, to eliminate the toxin effectively. There is no difference in the incidence based on socioeconomic status and sex.

The multiple strains of *S aureus* are classified by virulence factors and bacteriophage typing into four groups (I through IV). The toxin responsible for SSSS is produced by group II, strains type A and B.<sup>1</sup> The toxin gains systemic access through an infected lesion and targets the subepidermal layer of the skin. The exfoliative exotoxin leads to the cleavage of desmoglein 1 complex, an important desmosomal protein in the skin.

Of note, the same toxins that are responsible for SSSS also cause bullous impetigo. However, the toxin-induced bullae in SSSS are sterile, whereas the bullae in impetigo contain bacteria. There appears to be a relationship among the extent of disease, the amount of the toxin produced, and whether the toxin is released locally or systemically. As a result, a spectrum of disease exists, and likely milder cases of SSSS are undiagnosed.

### **Clinical Features**

Staphylococcal scalded skin syndrome usually presents with a prodrome of sore throat or conjunctivitis. The conjunctivitis can be severe, with both periorbital edema and purulent discharge. Within 48 hours, the patient typically develops fever, malaise, and extremely tender erythematous patches on the face, neck, axilla, and perineum. Flaccid bullae develop within the erythematous areas, and the Nikolsky sign is positive. The bullae initially affect the flexures because of the higher concentration of eccrine ducts that are prone to toxin effect, and occasionally large areas of the skin may be affected. The superficial bullae enlarge and rupture easily to reveal a moist, erythematous base, which gives rise to the scalded appearance.

Histopathologically, SSSS results in a superficial intraepidermal cleavage through the granular layer without epidermal necrosis and with very few inflammatory cells. This is unlike toxic epidermal necrolysis, in which the deeper cleavage through the skin is at the subepidermal layer and full-thickness necrosis of the epidermis is present.<sup>2</sup>

Isolation of *S aureus*, not from the bullae themselves (because these are a result of toxin, not direct infection) but rather from conjunctivae, skin folds, nares, umbilicus, and other affected sites, can guide the evaluation. However, such cultures are not diagnostic unless the specific strain with exfoliative toxin production can be identified. Histologic examination via skin biopsy is the most useful diagnostic tool and can be performed easily and painlessly without local anesthesia via a “skin snip” that involves removing the very superficial blister roof and sending it to a pathologist for a frozen section examination for rapid and effective exclusion of the deeper blistering disorders, specifically Stevens Johnson syndrome or toxic epidermal necrolysis.<sup>3</sup>

## Treatment

Prompt diagnosis and early treatment with parenteral antistaphylococcal antibiotics is essential. Although methicillin-resistant strains of *S aureus* (MRSA) associated with SSSS occasionally have been described, most cases of SSSS are a result of phage group II *S aureus*, in which multiresistance is rare.<sup>4</sup>

Blisters should be left intact. Eroded areas are covered best with white petrolatum-impregnated gauze, which helps reduce further trauma to the skin. A topical antibiotic ophthalmologic ointment is a helpful adjunct to systemic antibiotics to treat the conjunctivitis.

Patients should be treated initially in isolation to prevent infectious spread. Pressure-relieving mattresses may improve comfort and reduce pressure sores. Because the eroded skin is at risk of becoming secondarily infected, standard infection control measures should be practiced.<sup>5</sup>

Pain from the skin lesions is a major cause of morbidity. Adequate analgesia may require opioids. Thermal dysregulation due to underlying infection, severity of illness, and peripheral vasodilatation may occur. Therefore, the patient's core temperature and room temperature should be monitored and the room temperature altered as needed. Fluid and electrolyte losses can be considerable and need to be monitored carefully and replaced either orally or parenterally. When recovery is slow, nutrition support may be necessary. Application of topical mupirocin ointment to the nares, a common site for *S aureus* carriage, may help eradicate the carriage state to prevent recurrence.

## Prognosis

The duration of illness in SSSS is usually 7 to 10 days. Because of the superficial nature of the cleavage plane, the skin typically heals without scarring. Mortality in childhood SSSS is approximately 4% and is associated with extensive skin involvement, overwhelming sepsis, and the resultant electrolyte imbalance.

### Lessons for the Clinician

Staphylococcal scalded skin syndrome is a common exfoliative skin condition in children, and clinicians should have high index of suspicion due to the potential for significant morbidity and mortality. Clinically, Nikolsky sign (shearing superficial skin layers) is a key diagnostic feature. *S aureus* is the bacterial pathogen responsible for SSSS, and treatment with parenteral antibiotics is indicated. Although there are reports of MRSA causing SSSS, most cases are not due to resistant *S aureus*. Mupirocin topical ointment applied to the nares, a common site for *S aureus* carriage, can aid in eradicating the carriage state to prevent recurrence.

Kavita Thakkar, MD, Robin Gehris, MD, Noel Zuckerbraun, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA.

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## Newborn With Hemorrhagic Papulonodular Lesions

### Presentation

At birth, an otherwise healthy boy has blueberry muffin nodular-like lesions measuring  $0.5 \times 0.5$  cm at his right postauricular area, left neck skinfold, thigh, and groin (Figure 8.1). He also has a  $0.5 \times 0.5$  cm pustule on the dorsum of the foot (Figure 8.2). The infant has crusty lesions on the left side of his lip (Figure 8.3) and eyebrow, smaller bluish papules measuring  $0.25 \times 0.25$  cm (two on the back [Figure 8.4] and one at the preauricular area [Figure 8.5]), and two petechial lesions on the right frontal area. The rest of the physical examination findings are within normal limits.



**Figure 8.1.** Blueberry muffin macules on the thigh and groin.

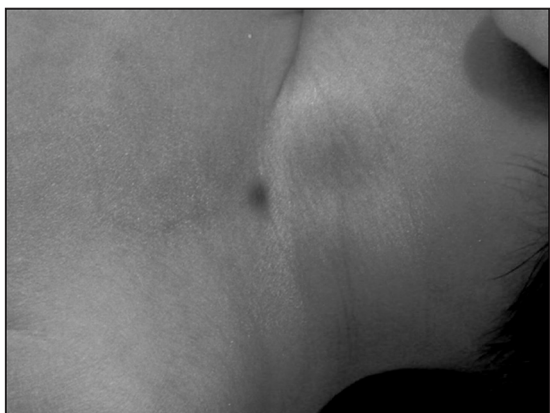




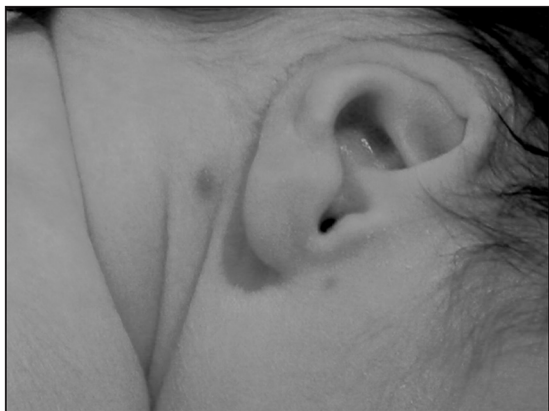
**Figure 8.2.** Erythematous vesicular lesion on the dorsum of baby's foot.



**Figure 8.3.** Crusted erythematous vesiculopustular lesion on the upper lip.



**Figure 8.4.** Two erythematous macules on the back of the infant.



**Figure 8.5.** Pre- and postauricular erythematous nodules.

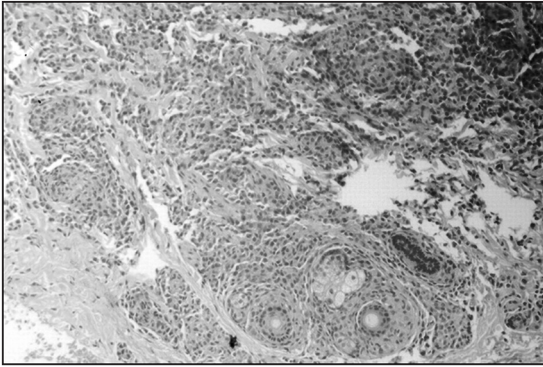
The infant was born to a 24-year-old G4P1 woman at 38 1/7 weeks' gestation. The mother has a history of smoking 1 pack of cigarettes per day during pregnancy. Apgar scores are 9 at both 1 and 5 minutes. Screening reveals blood group O+, hepatitis B surface antigen-negative, rubella immune, rapid plasma reagin-nonreactive, human immunodeficiency virus-negative, and group B Streptococcus-negative.

Initial laboratory analysis for the infant reveals a high white blood cell count with a left shift, elevated aspartate aminotransferase (124 U/L) and lactate dehydrogenase (1,299 U/L), and a normal C-reactive protein concentration. Gram stain from a specimen of the lesion is negative, and blood culture shows no growth after 3 days. Skin biopsy reveals the diagnosis.

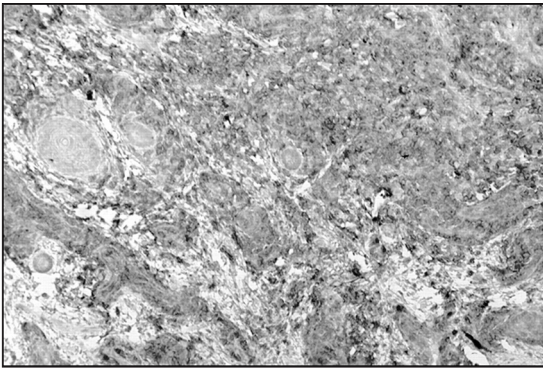
*Take a moment to consider the diagnosis in this infant.*

## Discussion

A skin punch biopsy is taken from the right preauricular, left neck, and left groin lesions. Biopsies are sent for hematoxylin and eosin staining, chromosome studies, neuroblastoma and N-myc gene amplification by fluorescent in situ hybridization, and flow cytometry for leukemia and lymphoma studies. Hematoxylin and eosin staining reveals Langerhans cell histiocytosis (Figures 8.6 and 8.7). Toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (TORCH) titers are ordered.



**Figure 8.6.** Skin biopsy showing diffuse dermal infiltration by atypical histiocytes. Note the infiltration around skin adnexa. Hematoxylin and eosin, original amplification  $\times 100$ .



**Figure 8.7.** Skin biopsy showing atypical dermal histiocytic infiltrate stained with immunoperoxidase for CD1a, which is 3+ positive. Original magnification  $\times 250$ .

## ***Differential Diagnosis***

The differential diagnosis of lesions as described for this infant include erythema toxicum neonatorum, transient neonatal pustular melanosis, miliaria, epidermolysis bullosa, epidermolytic hyperkeratosis, acropustulosis of infancy, cutaneous lesions of congenital candidiasis, bacterial sepsis, congenital syphilis, varicella infection, TORCH, and myeloproliferative disorders.

## ***The Condition: Cutaneous Histiocytosis***

Langerhans cell histiocytosis (LCH) comprises a group of idiopathic disorders characterized by the proliferation of specialized bone marrow-derived Langerhans cells (LCs) and mature eosinophils. In 1868, Paul Langerhans discovered the epidermal dendritic cells that now bear his name. The ultrastructural hallmark of the LC, the Birbeck granule, was described a century later. In this diverse group of disorders, monocytes, macrophages, and dendritic cells accumulate and infiltrate the affected tissues. The pathogenesis is unknown; an ongoing debate exists over whether this is a reactive or neoplastic process.

The clinical presentations vary greatly, ranging from mild to life-threatening. Langerhans cell histiocytosis initially was divided into eosinophilic granuloma (localized bone lesions), Hand-Schüller-Christian disease (multiple organ involvement with the classic triad of skull defects, diabetes insipidus, and exophthalmos), and Letterer-Siwe disease (visceral lesions involving multiple organs). Most recently, this designation was changed to LCH to reflect recognition of the primary cell involved and the pathophysiology of the disease. Normal histiocytes originate from pluripotent stem cells, which can be found in bone marrow. Under the influence of various cytokines (eg, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor- $\alpha$ , interleukin-3 and -4), these precursor cells can become committed and differentiate to become a specific group of specialized cells. Committed stem cells can mature to become antigen-processing cells, some with phagocytic capabilities. These cells include tissue macrophages, monocytes, dendritic cells, interdigitating reticulum cells, and LCs.

A fourth clinical entity termed congenital self-healing reticulohistiocytosis (Hashimoto Pritzker variant) has been described in which skin lesions are present at birth, accompanied in rare cases by systemic findings, and complete spontaneous involution occurs within 2 to 3 months. The congenital form of LCH manifests as skin lesions at birth or during the early postnatal period. Cutaneous, firm, red-brown nodules and ulceration occur early in life. Rarely, purpuric lesions occur with a blueberry muffin presentation, and symptoms of organ involvement also may occur. Papulonodules (1 to 10 mm in diameter) or vesicles and crusts may be scattered over the scalp, face, and, to a lesser extent, the trunk and extremities. The lesions may ulcerate. Lesions may be followed by residual hypopigmented or hyperpigmented macules. The congenital form of histiocytosis tends to resolve spontaneously within weeks to months. Although the absence of systemic disease at presentation and the tendency for disease resolution are favorable, long-term follow-up care to detect evidence of relapse or progression in affected patients is suggested.

### ***Diagnosis***

Histopathologically, the key to diagnosis is to identify the pathologic LCs, which resemble the normal LCs of the skin but are not dendritic. The pathologic LC consists of a large, ovoid, mononuclear cell that is 15 to 25 mm in diameter, with a folded nucleus, a discrete nucleolus, and a moderate amount of slightly eosinophilic homogeneous cytoplasm. When the indentation of the nucleus affects its center, it acquires a reniform pattern; if the indentation is peripheral, the nucleus has a coffee bean shape. The Birbeck granule is the distinctive ultrastructural hallmark of the LC that consists of an intracytoplasmic membranous body.

### ***Treatment***

Localized skin disease is treated best with moderate-to-potent topical steroids. In cases of severe cutaneous involvement, topical nitrogen mustard (20% solution) may be used, based on its easy administration, especially in outpatient settings, and lack of adverse effects. Psoralen plus ultraviolet A is another excellent treatment for cutaneous-only LCH.

### ***Complications***

Relapse in affected patients has been reported up to 5 years after the initial disappearance of the disease. Cutaneous lesions usually disappear by 3 months, leaving residual hypopigmentation. Infrequently, a case originally diagnosed as chronic focal LCH may progress to multifocal or even disseminated disease.

## Lessons for the Clinician

Neonates commonly have vesiculopustular lesions that can be mistaken easily for an infectious process, and the more classic “seborrheic” and “eczematous” lesions may be observed later in the course. In addition, congenital skin lesions have been described as papules, macules, or nodules, some with central crateriform ulceration (Figure 8.3), that are red, brown, blue, or yellow. Patients who have nodular lesions, whether congenital or later, generally have a better prognosis. Infants who have persistent seborrhea or eczematous lesions despite treatment require tests to rule out LCH. In 1989, the Histiocyte Society published guidelines for the management of patients who have LCH. They suggested the following minimum baseline studies: complete blood counts, including platelets; liver function tests; coagulation studies; chest radiography; skeletal surveys; and urine osmolality testing. It is suggested that these examinations be repeated at 6-month intervals if findings are normal. If findings are abnormal, further testing or appropriate follow-up is necessary. Bone scans, although less sensitive indicators of bony involvement, may provide complementary information.

*Hassan Ibrahim, MD, Guillermo Sangster, MD, Margaret E. Hollister, MD, Hilary Tice, PharmD, Enrique Gonzalez, MD, Diana Bienvenu, MD, Department of Pediatrics, Louisiana State University Health Science Center-Shreveport, Shreveport, LA.*

## COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER

Although congenital cutaneous LCH typically resolves on its own (as shown in this case), there have been 7 case reports that describe preterm infants with LCH who developed multisystemic disease with a high fatality rate.<sup>1</sup> The absence of E-cadherin cell expression may correlate with a severe clinical course. In 2009, the Histiocyte Society published updated guidelines for the evaluation and treatment of systemic LCH. Presence of Birbeck granules can now be determined by positive expression of Langerin within cells of the lesion instead of requiring direct evidence of ultrastructural cytoplasmic granules.<sup>2</sup> Abdominal ultrasonography should also be obtained at baseline to assess the size and structure of the liver and spleen.

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## **Term Neonate With Hypotension and Rash**

### **Presentation**

A 3.7-kg, 6-day-old term infant presents to the emergency department with decreased oral intake, irritability, and respiratory distress. No history of fever, or respiratory or gastrointestinal symptoms, are elicited. Prenatal and delivery history are unremarkable, including negative maternal serologies and group B *Streptococcus* testing. Mother is healthy, but the sibling has rhinorrhea and cough. The infant is intubated for respiratory distress and receives 60 mL/kg of normal saline boluses for poor perfusion, and dopamine is started for hypotension. The infant is noted to have a blanching, maculopapular erythematous rash involving the axilla and trunk, but otherwise has a nonfocal physical examination. A sepsis evaluation is performed, including blood, urine, and cerebrospinal fluid (CSF) cultures. Empirical antimicrobial therapy with ampicillin, gentamicin, and acyclovir is administered, and the infant is transferred to the neonatal intensive care unit (NICU) for further management.

### **Progression**

Cerebrospinal fluid analysis reveals 1 white blood cell and 760 red blood cells/mm<sup>3</sup>, glucose of 44 mg/dL, and protein of 95 mg/dL with a negative Gram stain. Laboratory results reveal lymphopenia (absolute lymphocyte count of 745) with normal platelets, normal liver transaminases, and C-reactive protein (CRP) of <0.5 mg/dL. Chest and abdominal radiographs are normal.

The patient has one documented fever to 38.2°C in the first 24 hours of hospitalization and is afebrile thereafter. Blood, urine, and CSF cultures are sterile at 48 hours, herpes simplex virus polymerase chain reaction (PCR) testing is negative, and, thus, antimicrobials are discontinued. Overall, the infant's condition improves, and the infant is extubated, pressors are discontinued, and oral feeding is initiated. However, the rash becomes more confluent and intensely erythematous, spreading



from the trunk to the abdomen and perineum. The infant is irritable when touched or moved. A tentative diagnosis of toxic shock syndrome is made, and therapy with clindamycin is initiated. Further diagnostics are obtained: respiratory viral PCR and enteroviral PCR testing and surveillance cultures for group A *Streptococcus* and *Staphylococcus aureus* are negative, and lymphopenia has resolved. An erythroderma-like rash in the setting of culture-negative sepsis prompted us to send a test that confirms the diagnosis.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

### Diagnosis

Reverse transcriptase PCR (RT-PCR) for parechovirus is ultimately positive from both whole blood and CSF. By hospital day 4, the rash begins clearing on the chest and abdomen and is less erythematous, with few papular erythematous lesions on the thighs. The infant is breastfeeding well and is discharged home.

### The Condition

Human parechoviruses (HPeVs) are single-stranded RNA viruses that belong to the family Picornaviridae, known to cause a variety of disease manifestations in humans. Human parechoviruses 1 and 2 were identified more than 50 years ago and were previously misclassified as enteroviruses (echo22 and 23). To date, 16 different genotypes of the virus have been discovered. Despite being a widespread pathogen affecting mainly young infants, HPeV is frequently underdiagnosed.<sup>1</sup> With the application of molecular diagnostic assays, however, HPeV is emerging as an important pathogen in neonates and infants.<sup>2</sup>

Infants with HPeV infection can present with a wide spectrum of illnesses, ranging from mild, self-limited gastrointestinal or respiratory tract infections to more severe diseases, such as meningoencephalitis and a sepsislike syndrome.<sup>3</sup> Human parechovirus 3 seems to be associated with more severe disease in neonates and young infants.<sup>4,5</sup> The primary site of HPeV replication and transmission is thought to be the respiratory and gastrointestinal tracts.

Our infant presented with a sepsislike syndrome and rash, requiring resuscitation and intensive care management. Retrospective reviews of cases involving infants with HPeV central nervous system infection found that the most common clinical presentation was indeed a sepsislike syndrome and that the most common symptoms were fever, irritability, and a nonspecific rash.<sup>6</sup> Dermatologic manifestations attributable to HPeV infection include erythrodermalike rash, erythematous maculopapules predominantly on the trunk, and a distinctive palmar-plantar erythema,

the latter being reported in febrile neonates and young infants with HPeV3 infection.<sup>4,5</sup> Compared with enterovirus infections, more infants with HPeV infection also required intensive care unit care.<sup>7</sup> Our patient had a normal CRP, had a low peripheral white blood cell count, and lacked CSF pleocytosis despite the presence of HPeV in both blood and CSF, as has been reported previously.<sup>3,6,7</sup>

Definitive diagnosis is made by RT-PCR testing specific for HPeV, but further viral sequencing is required to determine the HPeV type.

Management of infants with HPeV infection is mainly supportive.

### **Lessons for the Clinician**

Human parechovirus infections should be considered in the differential diagnosis of neonatal sepsis and meningitis. Testing of CSF and blood samples for HPeV is suggested as part of the sepsis diagnostic evaluation, especially for infants less than age 6 months presenting with fever and rash.

Lack of CSF pleocytosis and a normal or low white blood cell count and CRP can be seen with HPeV infections.

Clinicians should be aware that despite the clinical overlap between enterovirus and HPeV infections, HPeV is not detected on routine enterovirus PCR assays.

Human parechovirus RT-PCR assays can be performed on blood, CSF, nasopharyngeal, and rectal stool specimens. Timely results of HPeV RT-PCR may optimize clinical management of infants and possibly reduce the use of antibiotics and duration of hospital stay.

*Sushma Nuthakki, MD, Division of Neonatology, Monica I. Ardura, DO, Division of Infectious Diseases and Immunology, Department of Pediatrics, Nationwide Children's Hospital and The Ohio State University Medical Center, Columbus, OH.*

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### COMMENTARY BY DR JOSEF NEU, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE

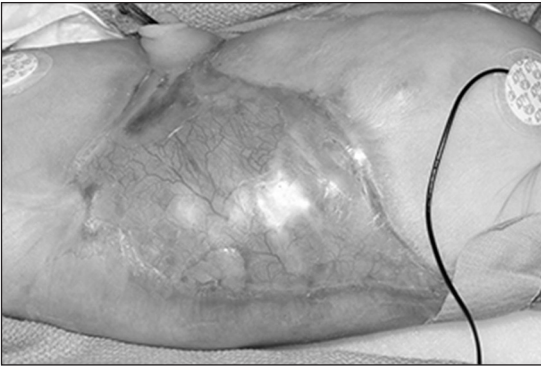
A recent review of NICU babies being investigated for late-onset sepsis utilized RT-PCR to evaluate the prevalence of HPeV infection and found that of 84 samples, 11 showed detectable HPeV.<sup>1</sup> Although it is not clear whether this was a cause of the symptoms that prompted the workup, it raises suspicion that we should be considering this more often. For the reader who wants to see more of how these lesions associated with this viral infection appear on brain imaging, please see Verboon-Maciolek MA, Groenendaal F, Hahn CD, Malgorzata A, et al. *Ann Neurol* 2008;64:266–273.

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## Large Skin Defect of the Trunk Noted at Birth

### The Case

A 1-day-old male infant is transferred to the neonatal intensive care unit (NICU) with a large congenital skin defect of the inferior chest and abdomen extending in a butterfly distribution to the flanks (Figure 10.1).



**Figure 10.1.** Well-demarcated butterfly-shaped lesion affecting skin, muscle, and fascia which spares the umbilicus. Photograph taken less than one day after birth.

### *Prenatal and Birth Histories*

39-year-old gravida 1 and para 1 mother.

Pregnancy originally had been a monochorionic/monoamniotic twin gestation, complicated by a fetal demise at 15 weeks.

Prenatal ultrasound had demonstrated slightly reduced abdominal circumferences, but no other abnormalities.

The pregnancy was additionally complicated by pregnancy-induced hypertension, which required magnesium sulfate.

The family denies any history of congenital anomalies or dermatologic disorders, including immunobullous disease.

There was no maternal history of tobacco, alcohol, or drug use. Mother is negative for HIV, hepatitis, rubella, and group B Streptococcus.

Delivery was by caesarean delivery because of failure to progress.

Apgar scores were 8 and 9 at 1 and 5 minutes, respectively.

Birthweight was 3.05 kg.

### ***Case Progression***

Heart rate: 139 beats/min

Respiratory rate: 61 breaths/min

Blood pressure: 79/42

Temperature: 37.1°C

Oxygen saturation: 99% on room air

Weight: 3.05 kg (19th percentile)

Head circumference: 35 cm (31st percentile)

Length: 48 cm (20th percentile)

### ***Physical Examination***

Head: Normocephalic, anterior fontanelle open, soft and flat, facial features symmetric and nondysmorphic, normal hair pattern.

Ear, nose, and throat: Ears normally formed, no cleft lip or palate, no lesions of oral mucosa.

Cardiovascular: Normal S1, S2; regular rate and rhythm; no murmur, quiet precordium.

Lungs: Clear, equal breath sounds; no retractions, not tachypneic.

Abdomen: Soft, nondistended, no organomegaly.

Genitourinary: Normal term male genitalia, no sacral dimple.

Skin: A well-demarcated, symmetric patch of atrophic skin is over the abdomen and inferior chest, extending to the midaxillary lines bilaterally in a butterfly distribution. The umbilicus is spared, as are the back, neck, extremities, and genitals. The

involved skin appears translucent, with apparent loss of the underlying dermis and muscle (Figure 10.1). Fibrous bands extend symmetrically from the shoulders and hips bilaterally to the area of concern (Figure 10.2). There is no nail dystrophy.

**Musculoskeletal:** Extremities are well formed.

**Neurologic:** Alert, active, normal tone, normal suck and rooting reflexes.



**Figure 10.2.** Fibrous band extending from skin defect to posterior upper arm. Photograph taken less than one day after birth.

## ***Imaging***

Head ultrasound: No evidence for any intracranial pathology.

Chest radiograph: Normal.

## ***Hospital Course***

Pediatric dermatology and plastic surgery were each consulted. Per their recommendations, the patient's skin defect was wrapped in petroleum jelly dressings, changed twice daily. He was maintained on broad-spectrum antibiotics and intravenous fluids.

## ***Differential Diagnosis***

Epidermolysis bullosa

Focal dermal hypoplasia

Aplasia cutis congenita

Setleis syndrome

*Take a moment to consider the diagnosis in this infant.*

## **Actual Diagnosis**

### ***Aplasia cutis congenita with fetus papyraceus***

## **The Experts**

Aplasia cutis congenita (ACC) is a rare disorder involving a well-demarcated absence of all skin layers over the affected area, often extending to involve the underlying muscle and bone. It can be extremely variable in its presentation, involving any area of the body. Most cases (85%) involve the scalp and in this presentation can extend to the dura mater. Lesions that have undergone some degree of healing in utero can appear as fibrotic scars.

Aplasia cutis congenita can be idiopathic, or it can be associated with various congenital anomalies (omphalocele, tracheoesophageal fistula, etc), congenital infections or teratogens, or genetic disorders (eg, Goltz syndrome). Distinct subtypes of ACC with characteristic patterns of skin involvement with or without other associated congenital anomalies have been classified by Frieden.<sup>1</sup>

Intrauterine demise of a monochorionic/monoamniotic twin is a recognized risk factor for aplasia cutis congenita. Infants who are affected by this form of the disorder often display a characteristic symmetric “butterfly-shaped” involvement of the trunk with fibrous bands surrounding the extremities, without involvement of the scalp. The macerated twin fetus (“fetus papyraceus”) is frequently found embedded in the placenta. Ten percent of ACC cases without scalp involvement are associated with a fetus papyraceus.<sup>2</sup> The combination of ACC in the characteristic distribution described above, along with the presence of placental infarcts or a fetus papyraceus, typifies Frieden class V.

Along with the skin defect, additional findings in such patients may include nail dystrophy, single umbilical artery, or clubbing of the hands and feet. Further complications may include developmental delay and or spastic paresis.

## **Pathogenesis**

Multiple theories have been suggested to explain the association between fetus papyraceus and ACC. A role for vascular anastomoses has been postulated in the pathogenesis of the disorder. One proposed mechanism suggests that thrombogenic material passing from the demised twin to the living twin could precipitate intravascular coagulation in the surviving twin, with consequences for the skin and soft tissue of the abdominal wall.<sup>3</sup> There has been a case report of ACC with hepatic hematomata, further suggesting a thrombotic/vascular event in the pathogenesis of this disease.

Altered hemodynamics between the living and deceased fetus may also play a role, as the relaxed vasculature of the deceased fetus may permit the blood to be diverted away from the survivor. Other possible factors in the pathogenesis of this disorder include placental infarctions or amniotic bands disrupting the developing skin.

## ***Diagnosis***

The diagnosis of ACC with fetus papyraceus is made on the basis of the history and presentation. Aplasia cutis can appear as part of the clinical manifestation of an array of genetic disorders, including several single gene and chromosomal disorders (eg, trisomy 13).

Among the entities included in the differential diagnosis are syndromes such as focal dermal hypoplasia (Goltz syndrome, an X-linked disorder characterized by linear atrophic patches, skeletal defects, and other ectodermal anomalies) or focal facial ectodermal dysplasia (characterized by skin atrophy at the temples, sometimes part of a larger constellation of symptoms, such as in Setleis syndrome).

Epidermolysis bullosa, a family of hereditary blistering disorders, also deserves consideration. This heterogeneous group of disorders frequently manifests with numerous patches of fragile skin, often presenting as denudation secondary to its removal via friction. This can be distinguished from ACC by its frequent involvement of numerous body segments, the presence of other ectodermal anomalies (such as nail dystrophy), and the presence of underlying structures, such as dermis and muscle.

## ***Management***

Acute management is centered on preventing infection, replacing increased insensible fluid losses, and pain control. With smaller lesions, ACC can be treated conservatively with topical dressings or barrier creams. For larger lesions, such as those frequently seen in conjunction with a fetus papyraceus, surgical treatment may be necessary. This can take the form of split-thickness or full-thickness skin graft or skin allograft.

Tissue expansion, either with an inflatable device or by mechanical tension, is also useful in managing large defects. Skin flaps can be used, but abnormal vasculature in the skin adjacent to these areas can cause complications. To avoid the risks of surgery in a neonate, it is often appropriate to manage conservatively until the child is more mature.

In the case of our patient, the patient's skin defect was wrapped in petroleum jelly dressings, changed twice daily. He had good oral intake and was rapidly weaned off intravenous fluids. Pain control was achieved with glucose water and



acetaminophen, with narcotics given shortly before dressing changes. He tolerated this regimen well, although a trial of Bactroban resulted in local skin irritation and thus was discontinued.

His family was taught how to perform the dressing changes at home, and he was discharged from the NICU after 12 days. Because his wound had epithelialized well during this time, he was judged not to need systemic or topical antibiotic treatment.

He was followed closely by both plastic surgery and dermatology. Six weeks after discharge, his wound was almost entirely regranulated (Figure 10.3), and he was above the 50th percentile for height and weight. At 4 months, he was able to sit with support, demonstrating good truncal stability, and at 12 months he was developing normally. Because of hypertrophic scarring over the defect, he required surgical release of the area, performed at age 12 months. His family was instructed on scar massage. At age 12 months, he continues to do well (Figure 10.4).



**Figure 10.3.** Granulation of skin defect at 6 weeks after birth.



**Figure 10.4.** Healed scar over skin defect at age 1 year.

## Summary

Aplasia cutis congenita is characterized by a focal absence of skin layers. A history of a deceased twin is a risk factor for ACC, and the macerated twin fetus (a “fetus papyraceus”) can frequently be found embedded in the placenta. In this context, the skin defect typically affects the abdomen and inferior chest, often in a butterfly distribution.

Pathogenesis is likely to involve vascular anastomoses between the surviving and deceased twin. Thrombogenic material may be passed through the circulation to the surviving twin (resulting in an intravascular coagulopathy and ensuing disruption of the developing skin) or alternatively through altered hemodynamics (whereby the surviving twin effectively exsanguinates into the deceased twin).

Treatment may be conservative, focusing on petroleum jelly dressing, maintaining hydration and nutrition, as well as pain and infection control. Surgical therapy (including skin grafts and or tissue expansion) may be necessary.

Daniel L. Kenney, MD, Dawn Marie R. Davis, MD, Christopher E. Colby, MD, Samir Mardini, MD, Steven L. Moran, MD, Mayo Clinic, Rochester, MN

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## **An Infant Who Develops an Erythematous Lesion on the Cheek**

At birth, a preterm newborn presents with right facial asymmetry and right ear deformity characterized by decreased cartilage, auricular cupping, and protuberance.

### ***Prenatal History***

31-year-old gravida 2 para 0-0-1-0 Caucasian mother who received regular prenatal care.

Blood type B-, antibody screen negative, hepatitis B antigen negative, rubella immune, group B Streptococcus screen not performed.

### ***Birth History and Initial Hospital Course***

Rupture of membranes occurred 45 hours prior to delivery with clear fluid. The mother received betamethasone and ampicillin prior to delivery. Due to transverse lie, delivery was by cesarean section. Apgar scores were 2 at 1 minute, 4 at 5 minutes, and 6 at 10 minutes. The infant's birthweight was 1,125 grams. The infant was intubated soon after delivery, and thick, yellow secretions were noted from the endotracheal tube.

Three doses of surfactant were administered over the first 24 hours after delivery. She had a relatively intense initial course, requiring high pressures on high-frequency oscillatory ventilation, with mean airway pressure as high as 25 torr. Hypotension necessitated the use of volume resuscitation and dopamine. An echocardiogram revealed evidence of pulmonary hypertension. Because the infant required 1.00 FiO<sub>2</sub>, inhaled nitric oxide therapy was initiated, to which she responded well, with weaning from ventilation over the following 3 to 4 days. She was extubated 4 days after birth to nasal continuous positive airway pressure and subsequently to nasal cannula 21 days after birth.

Due to the initial presentation, blood was drawn for culture, and the infant was started on ampicillin and gentamicin soon after delivery. Initial blood culture as well as endotracheal culture revealed no growth. C-reactive protein (CRP) levels were  $<0.2$  mg/dL, 1.0 mg/dL, and 0.4 mg/dL on the first, second, and third days after birth, respectively. Initial white blood cell count (WBC) was  $52.2 \times 10^3/\text{mCL}$  ( $52.2 \times 10^9/\text{L}$ ). Despite the negative cultures, the patient received 7 days of antibiotic therapy.

Head ultrasonography on the first and seventh days after delivery revealed no hemorrhage. Although initial echocardiography showed a patent ductus arteriosus, a subsequent evaluation 5 days after birth documented spontaneous closure.

Over the next several weeks, the infant progressed on feedings and was weaned to room air. At 8 weeks after birth, her weight was 2.4 kg.

### ***Case Progression***

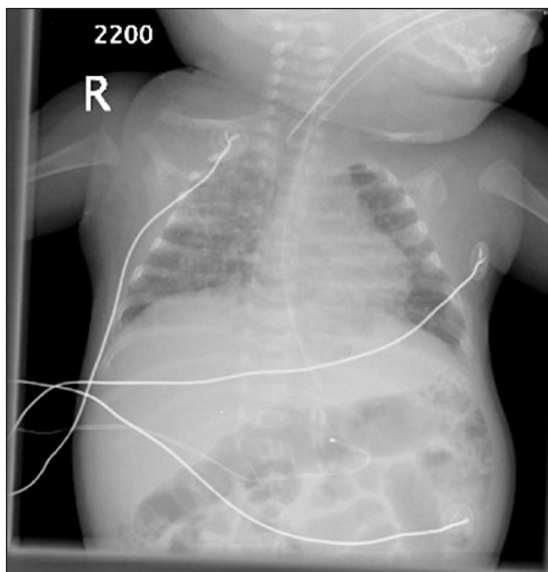
At 56 days after delivery, the infant was doing well on full enteral feedings of human milk with supplementation. She was stable in room air. Early in the morning, an erythematous lesion was noted over the right cheek (Figure 11.1).



**Figure 11.1.** Erythematous lesion over right cheek.

Over the next several hours, the infant developed increasing respiratory distress, progressing from nasal cannula to intubation and mechanical ventilation.

Chest radiograph revealed bilateral diffuse infiltrates (Figure 11.2).



**Figure 11.2.** Chest radiograph with bilateral diffuse infiltrates.

The erythema over the right face increased. Approximately 12 hours after initial presentation, the lesion had spread to the submental region, with areas of purple in the submental region and the right cheek. An area of fluctuance was noted over the right cheek (Figure 11.3).



**Figure 11.3.** Increasing erythema over right cheek.

### **Laboratory Findings**

WBC count of  $16.5 \times 10^3/\text{mCL}$  ( $16.5 \times 10^9/\text{L}$ ) with 50% segmented neutrophils, 20% lymphocytes, and 5% monocytes.

CRP of 0.9 mg/dL.

## ***Differential Diagnosis***

Skin trauma

Cellulitis

Chemical burn/dermatitis from topical therapy

Ludwig angina

Infected salivary gland

Infected lesion (bullous staph or herpes lesion)

(Adapted from Pickett and Gallaher, 2004)<sup>1</sup>

If this is an infectious process, what organism might be responsible?

*Escherichia coli*

Group B Streptococcus

*Pseudomonas aeruginosa*

*Staphylococcus aureus*

***Take a moment to consider the diagnosis in this infant.***

## Actual Diagnosis

### *Group B Streptococcus Sepsis and Cellulitis*

The blood culture grew group B *Streptococcus* at about 12 hours. The CRP concentration was 9.1 mg/dL at that time. The patient's respiratory distress continued to progress, with the need for high pressures, and high-frequency oscillatory ventilation was initiated with 1.00 FiO<sub>2</sub> and a mean airway pressure of 20 torr. Nitric oxide therapy also was added. Due to the infant's clinical instability, a lumbar puncture was not performed. A 2-g/kg dose of intravenous immune globulin was administered.

Surgical consultation was obtained. Due to the progressive nature of the lesion as well as the worsening clinical condition despite treatment with antibiotics for more than 24 hours, the lesion was debrided surgically. Areas of necrosis were found in the dermal region, but the fascia was intact (Figure 11.4).



**Figure 11.4.** Right cheek with areas of necrosis and intact fascia following surgical debridement.



The infant's clinical condition remained critical for the next several days, but improved thereafter. The CRP level decreased to 1.4 mg/dL at 6 days after surgery. A computed tomography scan of the facial bones showed no sign of erosion or osteomyelitis. At 1 month following the initial presentation, the wound had essentially closed without further surgical intervention (Figure 11.5).



**Figure 11.5.** Right cheek one month after surgery.

## The Experts

Although it is relatively uncommon, late-onset group B *Streptococcus* (GBS) infection can present as cellulitis. When cellulitis occurs, it is often on the face, with buccal, submandibular, and submental involvement. This may be related to the close proximity of mucous membrane colonization. Several reports also have described ipsilateral otitis media with cellulitis.<sup>1</sup> Other areas of involvement have included the retropharynx, inguinal region, perineum, and lower abdomen. A review of the cases described in the literature reveals that infants born preterm may be at higher risk for this process.<sup>2</sup>

Group B *Streptococcus* also has been implicated in necrotizing fasciitis in six adults and one child. Risk factors include diabetes, trauma, or preceding surgery. Necrotizing fasciitis in neonates is relatively rare but has been described in the literature. Most commonly, it involves the abdominal wall, but it can affect the thorax, back, scalp, and extremities.<sup>3</sup> Necrotizing fasciitis usually is a secondary process that occurs after omphalitis, mammitis, or bullous impetigo. It typically has a polymicrobial etiology, often including *Staphylococcus aureus* as well as *Clostridium* and *Bacteroides* spp. However, both group A *Streptococcus* and, more recently, methicillin-resistant *Staphylococcus aureus* have been implicated in severe necrotizing fasciitis.

In both cellulitis and necrotizing fasciitis, the first sign of infection generally is erythema over the affected area. Subsequently, the skin becomes indurated and warm. Fever is generally not present. Usually there are accompanying signs of generalized sepsis and often patients who had been previously well require respiratory support. The lesion progresses rapidly to cover much of the face or other affected area.

### **Late-onset Group B *Streptococcus* Infection**

Since the introduction of the Centers for Disease Control and Prevention's guidelines to reduce perinatal transmission of GBS, there has been a decrease in early-onset GBS sepsis. However, the incidence of late-onset GBS infection has remained constant. It is important to note that despite initial treatment with ampicillin and gentamicin during the first week after birth, this child remained vulnerable to late-onset GBS infection.

Most patients respond well to antibiotic therapy. Therapy can be directed at the specific organism if detected in blood culture. It is important to obtain cerebrospinal fluid for analysis because GBS commonly causes meningitis. However, this may not be possible at the initial presentation if the patient is clinically unstable.

Pathogenic type III group B *Streptococcus* has an increased adherence to the mucosal epithelium in colonized neonates and may not be eradicated by a full course of antibiotic therapy. Recurrent GBS infections can occur in hospitalized neonates. This patient's serotype returned as type Ia/c.

Henry C. Lee, MD, David K. Hong, MD, Stanford University Medical Center, Stanford, CA

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## Seizure-like Symptoms in a 2-Day-Old Term Girl

### The Case

A 2-day-old term female infant was noted to have lip smacking, eye twitching, and abnormal “jerking” left arm and leg movements. A loading dose of phenobarbital was given, but the episodes progressed to generalized clonic movements associated with apneas and desaturations requiring intermittent bag mask ventilation. A repeat dose of phenobarbital and a loading dose of phenytoin were given.

A sepsis workup including complete blood cell count and blood culture was performed. A lumbar puncture was planned but was deferred because of the infant’s acutely deteriorating status.

She was started on empiric antibiotics and acyclovir before ventilation for transfer to a tertiary referral hospital for further evaluation and management. Soon after arrival, a confluent erythematous rash presenting in a linear pattern was noted on the legs and lower trunk (Figures 12.1 and 12.2).



**Figure 12.1.** Development of rash at 44 hours after birth.



**Figure 12.2.** Leg rash presents in a linear pattern.

### ***Prenatal History***

30-year-old G4P3 now 4.

Good prenatal care.

Fetal ultrasound results normal.

Maternal history significant for depression (on Lexapro), mild mental retardation, incontinentia pigmenti in mother and female sibling (not known at time of transfer).

No known history of herpes infection.

### ***Birth History***

Labor was spontaneous.

Delivered vaginally with no resuscitation required.

Apgar scores were 9 at 1 min and 9 at 5 min.

Birthweight: 3,390 g.

Head circumference: 35.9 cm.

### ***Case Progression***

Initial examination revealed a nondysmorphic, appropriate-for-gestational-age infant intubated and sedated on a ventilator. Anterior fontanelle noted to be full but soft. On neurologic examination, infant was noted to have generalized hypertonia, increased deep tendon reflexes, and bilateral ankle clonus. Rash, as seen in the figures, was nonvesicular in nature.

Infant continued to have intermittent seizure activity associated with vital sign changes (bradycardia, desaturations, and apnea) confirmed on electroencephalogram. Midazolam bolus was given and infusion was started to control seizures. Phenobarbital levels and phenytoin levels were 236 mcmol/L (54.3 mg/L) and 64 mcmol/L (16.2 mcg/L), respectively.

### ***Laboratory Studies***

White blood cell count:  $8.34 \times 10^3/\text{mCL}$ , 71% neutrophils, 17% lymphocytes, 5% eosinophils

Hemoglobin: 16.3g/dL; hematocrit: 44.8%

Platelet count:  $144 \times 10^3/\text{mCL}$

Serum urea nitrogen: 1.6 mmol/L (4.49 mg/dL); creatinine: 36 mcmol/L

Calcium: 2.16 mmol/L (8.66 mg/dL); ionized calcium: 1.19 mmol/L

Base deficit: 1.1

Urine drug screen negative

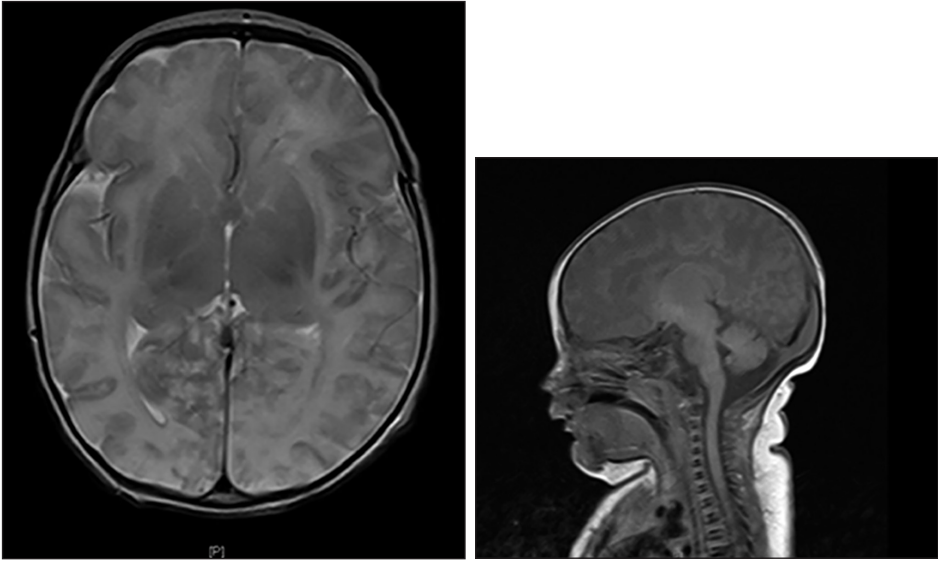
Plasma amino acids, ammonia, and lactate levels were all normal

### ***Radiographic Studies***

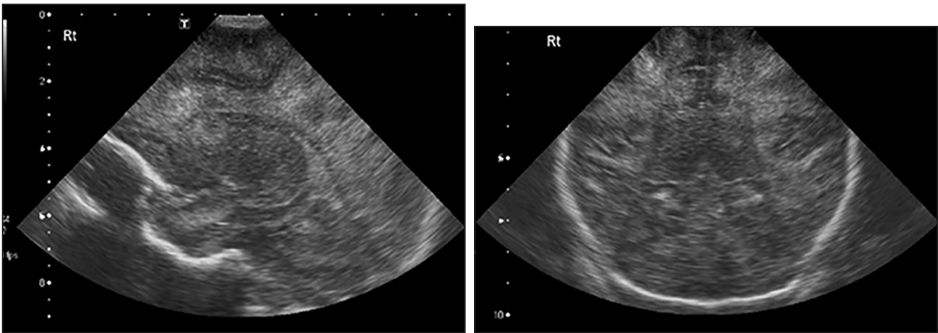
Magnetic resonance imaging (Figure 12.3) performed on same day of transfer revealed extensive bilateral cerebral infarcts, sparing cerebellum and brain stem.

Head ultrasound (Figure 12.4) showed no intracranial hemorrhages and normal-size ventricles.

Electroencephalogram done after phenobarbital and phenytoin loads showed multifocal epileptiform discharges most prominent in the left central region with some brief periods of suppression.



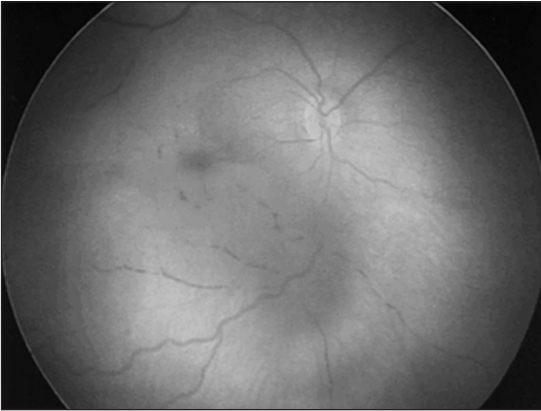
**Figure 12.3.** Magnetic resonance imaging of brain shows extensive cerebral infarction, sparing the cerebellum and brainstem. Few patchy areas of restricted diffusion noted in the basal ganglia. Extensive T1 hypointensity and T2 hyperintensity visible in the regions of restricted diffusion. There are some patchy areas of susceptibility on gradient echo scanning at the vertex, indicating hemorrhage. The corpus callosum is diffusely hypoplastic. Magnetic resonance angiogram shows no evidence of stenosis or occlusion in major vessels. Lactate peaks in basal ganglia consistent with cellular necrosis.



**Figure 12.4.** Head ultrasound images show narrowed cerebral ventricular system with no focal intracranial hemorrhages seen.

### ***Eye Examination***

Avascular areas in the periphery of right retina and a cherry red spot at the macula, likely infarction/vascular occlusion (Figure 12.5). Swollen optic disc, no retinal detachment. Prognosis for vision for right eye was thought to be poor.



**Figure 12.5.** Avascular areas in the periphery of right retina and a cherry red spot at the macula, likely infarction/vascular occlusion.

### ***Differential Diagnosis***

Neonatal herpes encephalitis

Neonatal stroke

Incontinentia pigmenti with neurologic involvement

Metabolic disease with encephalopathy

Florid erythema toxicum

*Take a moment to consider the diagnosis in this infant.*



## Actual Diagnosis

### *Incontinentia Pigmenti*

## The Experts

Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome, is an X-linked dominant neurocutaneous disorder that affects the skin, central nervous system, eyes, teeth, hair, nails, and skeletal system.

Incontinentia pigmenti is associated with mutations in the *IKBKG* gene (previously known as the *NEMO/NF-B* essential modulator gene), in which a large-scale deletion of exons 4 to 10 is present in up to 80% of affected individuals. Other mutations are small insertions or deletions of the gene.

Incontinentia pigmenti is rare, with 900 to 1,200 affected individuals reported to date. There is a family history in the mother in 30% of cases, while 68% are thought to be sporadic, with germline mutations inherited from the father in >80%.

The *IKBKG* gene is central to many immune, inflammatory, and apoptotic pathways and is found to confer protection against tumor necrosis factor–induced apoptosis.

Characteristic skin lesions evolve through 4 stages:

Stage 1 (blistering stage): occurs from birth to ~4 months of age. Erythema with vesicle-discolored skin involving the trunk and extremities, distributed in irregular, marbled, or wavy lines.

Stage 2 (verrucous stage): from ~4 months to ~6 months of age. Wart-like rash for several months.

Stage 3 (hyperpigmented stage): from ~6 months into adulthood. Swirling macular hyperpigmentation, with irregular areas of skin pigmentation along the lines of Blaschko.

Stage 4 (atretic stage): occurs during adulthood. Scarring, hypopigmentation, and localized alopecia.

Incontinentia pigmenti commonly affects other cutaneous systems besides skin. Alopecia may occur on the scalp, sometimes corresponding to areas of scarring from previous blistering in Stage 1. Hair, including eyelashes and eyebrows, may be sparse and thin. Mammary tissue anomalies also have been reported, ranging from aplasia of the breast to supernumerary nipples. Dentition can be affected with hypodontia, microdontia, abnormally shaped teeth, delayed eruption, or impaction. Nails can be dystrophic (mostly seen during Stage 2), which is mostly transient, although presentation often may resemble onychomycosis.

Neurologic abnormalities in IP are less common, involving up to 30% of patients in major retrospective studies. Neonatal seizures and or encephalopathy are a common presentation with subsequent developmental delays and or cerebral palsy. Magnetic resonance imaging changes have been observed with extensive cortical necrosis, followed by cystic lesions, atrophic basal ganglia, and no progress in myelination in repeat scans.

The neonatal cerebral infarction in IP is thought to be a microvascular vaso-occlusive event. Up to 77% of affected individuals have some ophthalmologic manifestation, including 43% with vision-threatening problems. These include retinal detachment (which usually happens before age 6 years), phthisis bulbi, retinal ridges, severe myopia, optic atrophy, and strabismus. Less serious ocular involvement includes retinal pigment epithelial defects and corneal opacities.

Diagnostic clinical criteria for IP have been developed (at least one of the major criteria: typical skin lesions occurring in stages from infancy to adulthood, retinal disease, or evidence of IP in at least 1 first-degree relative with supporting minor criteria of teeth, hair, nails, and retina findings). Complete absence of minor criteria should raise doubt regarding the diagnosis. Skin biopsy demonstrates a spongiotic dermatitis with many eosinophils and large dyskeratotic cells during the vesicular stage. *IKBKG* is the only gene known to be associated with IP; targeted mutation analysis, sequence analysis, and X-chromosome inactivation studies can be performed. However, failure to identify an *IKBKG* mutation does not rule out the diagnosis.

Because IP is inherited in an X-linked dominant manner, male conceptuses who are affected with a loss-of-function mutation of *IKBKG* miscarry. Only those with 47,XXY karyotype or somatic mosaicism for the common *IKBKG* deletion may survive. Hence, the expected ratio among live-born children is one-third unaffected female, one-third affected female, and one-third unaffected male. The prognosis for IP in females is generally good with poor outcomes related to neurologic or ophthalmologic complications. Incontinentia pigmenti is considered a chromosomal instability syndrome, and breakage, if it occurs, places the patient at increased risk for developing malignancies.

The lack of vesicular skin lesions in stage 1, as in this case, can occur, and confirmation of the rash could be obtained by skin biopsy; however, the lesions did progress to hyperpigmentation, and this combined with the family history and the eye and central nervous system findings confirmed the diagnosis clinically.

## Case Follow-Up

The infant was slowly weaned off the midazolam drip. Seizure was well controlled with maintenance phenobarbital and phenytoin. She was extubated and started on gavage feeds because of poor suck. This infant was discharged from the hospital with neurology and genetics follow-up.

Juin Yee Kong, MD, John Smyth, MD, Anne Turner, MD, Royal Hospital for Women and Sydney Children's Hospital, Randwick, Sydney, Australia

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*Part 3*

# **Endocrinology**

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## **Five-Day-Old With Recurrent Hypoglycemia**

### **Presentation**

Five days after birth at a private hospital, an infant is brought to another hospital because he is inactive and limp. The delivery was by outlet forceps after a supervised, normal pregnancy to consanguineous (uncle-niece) parents. His birthweight was 3.25 kg. According to his parents, he did not cry until 1 hour after birth, was limp, fed poorly, and a few hours later, had cyanosis of lips and nails and generalized tonic and clonic convulsions that were unresponsive to anticonvulsants and intravenous (IV) glucose. The parents were told that he had hypoxic brain injury and possibly an intracranial hemorrhage. The convulsions became less frequent once expressed human milk was provided through a nasogastric tube. The exact details of management at the private hospital are not available.

The infant is the first child of the woman, who is well nourished and does not have diabetes. His weight on admission at 5 days of age is 3.66 kg, length is 49 cm, and head circumference is 33 cm. He is inactive and limp. His temperature is 97.8°F (36.6°C) and heart rate is 170 beats/min. His cry is feeble and response to pain is minimal. His anterior fontanelle is normal, hydration is adequate, Moro reflex is incomplete, and sucking and rooting reflexes are poor. He does not have syndromic features or acidosis. No additional findings are revealed in the remainder of the general and systemic evaluations.

The results of a complete blood count; measurement of electrolytes, calcium, and bilirubin; review of the cerebrospinal fluid (CSF) and urinalysis; electrocardiography and radiography of the chest and skull; and abdominal ultrasonography are normal. Cultures of blood, CSF, and urine are sterile. Oxygen saturation is 98%. Blood glucose on admission is 41 mg/dL (2.28 mmol/L) and is monitored every 1 to 4 hours. Urine ketones are negative.

The baby experiences recurrent episodes of biochemical hypoglycemia despite administration of a glucose infusion at the rate of more than 15 mg/kg per minute, boluses of glucose whenever hypoglycemic episodes occur, and hourly nasogastric feedings of expressed human milk. However, he becomes active and alert, and all the previously noted symptoms disappear. Any attempt at reducing the concentration of IV glucose results in a precipitous fall in blood glucose concentrations. He is gaining weight at a rate of about 54 g/d. A specific investigation suggests the diagnosis.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

### *Diagnosis and Differential Diagnosis*

Because the possibility of persistent hyperinsulinemic hypoglycemia of infancy (PHHI) was considered, insulin:glucose assays were performed on 11 blood samples (Table 13.1). Persistent hyperinsulinemic hypoglycemia of infancy was diagnosed based on clinical findings, refractory hypoglycemia despite administration of a glucose infusion at the rate of more than 10 mg/kg per minute, rapid weight gain, prompt resolution of symptoms with administration of glucose and frequent feeding, absence of other abnormalities, and an insulin:glucose ratio of more than 0.4 (0.65 to 3.08) at hypoglycemic and normoglycemic blood glucose concentrations.

**Table 13.1.** Insulin:Glucose Ratios for the Infant

Sample No.	Blood Glucose (mg/dL) (mmol/L)	Insulin Concentration (mcU/mL)	Insulin:Glucose ratio
1	27 (1.5)	19.6	0.73
2	44 (2.4)	33.6	0.76
3	29 (1.6)	30	1.03
4	28 (1.6)	19.4	0.69
5	59 (3.3)	26.5	0.49
6	30 (1.7)	70.5	2.35
7	29 (1.6)	39.5	1.36
8	37 (2.1)	69.2	1.87
9	40 (2.2)	26	0.65
10	41 (2.3)	62.5	1.52
11	44 (2.4)	135.4	3.08

Asphyxia could cause a state of persistent hyperinsulinism, but the infant subsequently attained the developmental milestones appropriate for his age when followed up until 3 years of age, ruling out the possibility of any significant degree of asphyxia. He did not have features of Beckwith-Wiedemann syndrome, cortisol deficiency, glycogen storage disease, defects in fatty acid oxidation, or Münchausen syndrome by proxy.



Plasma ketones, free fatty acids, ammonia, lactate, pyruvate, amino acids, carnitine, and acyl carnitine may be estimated to rule out other conditions. Metabolic screening results would be expected to be negative for this child. Cortisol and growth hormone concentrations are elevated during hypoglycemia, but otherwise normal. Ultrasonography, computed tomography scans, and magnetic resonance imaging occasionally may be useful in identifying a focal adenoma. Catheterization of portal and pancreatic veins for venous sampling of glucose, insulin, and C-peptide may be used to differentiate between focal and diffuse disease. Intraoperative histologic studies may be necessary to identify focal disease. Positron emission tomography with [18F]-Fluoro-L-DOPA is a promising method of differentiating focal from diffuse disease.

### ***Persistent Hyperinsulinemia Hypoglycemia of Infancy (PHHI)***

Persistent hyperinsulinemia hypoglycemia of infancy is a condition in which insulin is released inappropriately for the concentration of glycemia. Most cases are sporadic. The failure to reduce insulin secretion during hypoglycemia probably is due to structural or molecular abnormalities in the insulin secretory or glucose-sensing mechanisms. High insulin concentrations promote glycogenesis in the liver and skeletal muscle and reduction in free glucose and free fatty acids, resulting in hypoglycemia and neuroglycopenia.

There are two types of histologic abnormalities in PHHI. Diffuse abnormality of the islet cells is seen in 66.6% to 75% of cases. Mutations in the sulfonyl urea receptor and inwardly rectifying potassium channel may be responsible in fewer than 50% of cases. Focal adenoma is seen in 25% to 33.3% of cases, probably due to loss of maternal alleles in the imprinted chromosome region 11p15 in the adenoma, starting in a single pancreatic cell in the fetus.

Focal adenoma, seen commonly in the tail and body of the pancreas, usually is solitary and occasionally is multifocal. It may be too small to be palpated or identified by imaging studies. Islet-like cell clusters that have ductoinsular complexes, hypertrophic cells with giant nuclei, well-developed endoplasmic reticulum, and prominent Golgi complex are seen. Histochemical stains show increased insulin-containing cells. The rest of the pancreas is normal. In the diffuse form, similar findings are seen throughout the pancreas, which appears normal macroscopically.

In familial cases, the inheritance could be autosomal recessive or dominant, involving one of the following four genes: *SUR1*, *KCNJ11*, *GCK*, or *GLUD1*.

The incidence of PHHI is approximately 1 in 50,000 and 1 in 2,500 live births in populations of random mating and high rates of consanguinity, respectively. There is a slight increase in incidence in males. The presentation usually is from birth to 18 months, although rarely the onset is seen in adulthood.

The infants present soon after birth with persistent symptoms of hypoglycemia: lethargy, limpness, cyanosis, apathy, jitteriness, subnormal temperature, tachycardia, apnea, and seizures. Older infants also exhibit increased sweating and behavioral changes. Continuous high concentrations of IV glucose and frequent feedings alleviate symptoms promptly. With such treatment, the rate of weight gain is much higher than normal. Physical findings are unremarkable during euglycemia. Features of dysmorphism, ketosis, acidosis, and visceromegaly suggest other causes of hypoglycemia.

The European Network for Research into Hyperinsulinism (Aynsley-Green, 2000) has developed a consensus document on PHHI. They recommend prompt management of hypoglycemia with continuous glucose infusions and frequent feeding.<sup>1</sup> Glucagon may be used during hypoglycemia to increase the blood glucose concentrations. The drugs used to suppress insulin release are diazoxide, octreotide (a somatostatin analog), and nifedipine. The response to these drugs varies, and all have undesirable adverse effects. Typically, 95% or near-total pancreatectomy is necessary, although the drugs may help to postpone surgery.

Indications for surgery are failure of medical therapy to maintain euglycemia, identification of focal disease, or the preference of the infant's family for surgery. Focal lesions should be ruled out before and during surgery using multiple techniques to prevent extensive resection of pancreas.

Problems after surgery include initial failure to control hypoglycemia and subsequent development of diabetes mellitus and exocrine pancreatic deficiency, necessitating insulin and exocrine pancreatic supplementation. Long-term follow-up is essential in all children. Cryopreservation of the removed islet cells may be an option for possible autotransplantation later, if necessary.

The infant in this case was not given a trial of medical therapy; his parents opted for surgical management. Near-total pancreatectomy was performed on the 34th post-natal day. The histopathology of the excised pancreatic tissue was consistent with PHHI, diffuse type. He made an uneventful recovery except for hyperglycemia without ketonuria intraoperatively and during the first week after surgery, possibly due to the pancreas being in a state of surgical shock during and soon after surgery. He continues to be euglycemic, has not required insulin or exocrine pancreatic supplementation, and has experienced normal growth and development with follow-up of 3 years.

## Lessons for the Clinician

Persistent hyperinsulinemia hypoglycemia of infancy is an important, although rare, cause of hypoglycemia in early infancy. It can be diagnosed clinically, although the symptoms of hypoglycemia mimic hypoxic-ischemic brain injury, intracranial hemorrhage, or sepsis. A combination of seizures, subnormal temperature, irritability, cyanosis, apathy, tachycardia, hypotonia ("limpness"), apnea, prompt resolution of symptoms with treatment, requirement of higher-than-normal glucose infusion rates to maintain euglycemia, and greater-than-normal weight gain suggest the condition. An insulin:glucose ratio of more than 0.4 is highly suggestive. Regular blood glucose monitoring is essential before, during, and after medical and surgical therapy. Early diagnosis is critical to avoid death or permanent brain damage due to prolonged, severe hypoglycemia that can lead to developmental delay, recurrent seizures, and irreversible mental retardation.

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*Padmini Venkataramani, formerly of Ramana Gounder Medical Trust Hospital, Thudiyalur, Coimbatore, India, and currently of Department of Paediatrics & Child Health, FMHS, UNIMAS, Kuching, Sarawak, Malaysia; Pava A. Ganesan, Department of Paediatric Surgery, PSG Institute of Medical Sciences and Research, Coimbatore, India.*

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**COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER**

Not surprisingly, additional genetic abnormalities with congenital hyperinsulinism have been identified since publication of this case in 2007. At present, genetic causes are found in ~50% of affected patients. These defects occur in 11 different genes that regulate insulin secretion from the pancreatic beta cells, including the most common and severest forms: *ABCC8* and *KCNJ11*.<sup>1,2</sup> Unfortunately, diazoxide is not effective in the hypoglycemic treatment of most patients with mutations of these 2 genes. For diazoxide-unresponsive infants, genetic mutation analysis is recommended to quickly determine the most appropriate treatment (ie, octreotide, localized excision, or near-total pancreatectomy) and minimize brain injury. New medical strategies are currently being investigated, including glucagon-like peptide receptor antagonists, mammalian Target of Rapamycin inhibitors, and long-acting somatostatin analogues.<sup>3</sup>

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## **5-Week-Old Dehydrated Infant With Increased Urine Output**

### **Presentation**

A 5-week-old previously well female infant born at 41 weeks gestational age presents to the pediatric emergency department (ED) in the winter with a 2-day history of poor feeding. Her mother is concerned that the baby is more tired than usual, “is not getting enough to eat,” and is having difficulty latching on to the breast.

The mother explains that 2 weeks ago, the infant developed a dry cough and began having emesis after each feeding. She describes the emesis as nonbilious and nonbloody and approximately 1 ounce. An outside pediatrician prescribed a cough and cold medication and told the mother that the emesis was “normal baby spit-up.” Three days ago, the infant developed projectile vomiting immediately following each feeding.

Today, the mother reports that the infant is breathing much harder and deeper than usual, with continued and more frequent coughs. She describes the cough as paroxysmal, although the infant experiences no color changes. The mother is concerned that her baby does not look like herself and is difficult to arouse.

A review of systems reveals that the baby has not taken any human milk today, although her urine output has remained the same, with heavy, wet diapers. Her 2-year-old sister, who attends child care, has a cough and upper respiratory tract infection. The infant has no diarrhea, and her bowel movements are normal. There were no complications during the pregnancy. Her birthweight was 2,722 g, and she has been gaining weight appropriately, although the mother describes her as “scrawny” at birth.

Physical examination of the infant in the ED shows a temperature of 37.6°C, a heart rate of 173 beats/min, a respiratory rate of 50 breaths/min, and an oxygen saturation of 100% on room air. She appears tired but arousable and is crying without tears. She is dehydrated, with a mildly sunken anterior fontanelle, sunken eyes, dry

lips, and tacky mucous membranes. The baby has visible tachypnea with suprasternal and subcostal retractions, although lung sounds are clear; she has an audible dry cough. Cardiac examination reveals tachycardia but no murmurs, gallops, or rubs. The abdomen is soft, and no masses are appreciated. Her extremities are warm, although capillary refill is sluggish at 3 seconds. There is no evidence of trauma on examination.

Following placement of an intravenous line, the baby is given a 20-mL/kg bolus of normal saline. Laboratory tests include a blood gas, complete blood count, basic metabolic panel, liver function tests, blood culture, and catheterized urine for urine culture. Albuterol treatment via nebulizer is started for respiratory distress. Chest radiography is performed, and a rapid respiratory panel is ordered, including swabs for *Bordetella pertussis*. Abdominal ultrasonography is ordered because of concern for pyloric stenosis or intussusception. A laboratory test reveals the diagnosis.

## Discussion

### *Differential Diagnosis and Case Progression*

The differential diagnosis of an ill-appearing infant is very broad (Table 14.1). Numerous disorders may cause an infant to appear septic, the most common of which include certain bacterial infections and viral syndromes. However, the remaining disorders demand diagnostic consideration because they are potentially life-threatening, yet treatable.

*Take a moment to consider the diagnosis in this infant.*

Because of the time of year, the initial thought was that the infant had an infectious respiratory process. However, as the laboratory values became available, the diagnosis became clearer. The initial venous blood gas had a pH of 6.93 and base excess of  $-24$  mEq/L. Initial chemistry showed a sodium of 146 mEq/L (146 mmol/L), potassium of 7.0 mEq/L (7.0 mmol/L), chloride of 111 mEq/L (111 mmol/L), bicarbonate of less than 6 mEq/L (6 mmol/L), blood urea nitrogen of 26 mg/dL (9.3 mmol/L), creatinine of 0.7 mg/dL (61.9  $\mu$ mol/L), and glucose of 774 mg/dL (43.0 mmol/L). The diabetic ketoacidosis (DKA) experienced by the infant was the first presentation of neonatal diabetes mellitus. The tachypnea was attributed to Kussmaul breathing and severe metabolic acidosis.

Aggressive fluid resuscitation was continued in the ED. An insulin drip was started at 0.05 units/kg per hour, with fingerstick tests and blood gases monitored hourly. The baby was transferred to the pediatric intensive care unit for further management of severe DKA. Half of the deficit was replaced over the first 8 hours and the rest over the next 24 hours, assuming 15% dehydration. On the second hospital day, the insulin drip was discontinued, subcutaneous injections of insulin started, and oral feeding resumed. The baby resumed normal activity with excellent perfusion and maintained fingerstick glucose values in the normal range with adjustments in the insulin regimen. She was discharged from the hospital on the seventh hospital day with a follow-up endocrine appointment after her mother received extensive diabetic education.



**Table 14.1. Differential Diagnosis of the Ill-Appearing Infant**

Infectious Disease <ul style="list-style-type: none"> <li>• Bacterial sepsis</li> <li>• Meningitis</li> <li>• Urinary tract infection</li> <li>• Viral infections: enterovirus, respiratory syncytial virus, herpes simplex virus</li> <li>• Pertussis</li> <li>• Bronchiolitis</li> </ul>
Cardiac Disease <ul style="list-style-type: none"> <li>• Congenital heart disease</li> <li>• Supraventricular tachycardia</li> <li>• Myocarditis</li> </ul>
Endocrine Disorders <ul style="list-style-type: none"> <li>• Congenital adrenal hyperplasia</li> <li>• Neonatal diabetes</li> </ul>
Metabolic Disorders <ul style="list-style-type: none"> <li>• Hyponatremia, hypernatremia, hypoglycemia</li> <li>• Cystic fibrosis</li> <li>• Inborn errors of metabolism</li> <li>• Drugs/toxins</li> </ul>
Gastrointestinal Disorders <ul style="list-style-type: none"> <li>• Acute gastroenteritis with dehydration</li> <li>• Pyloric stenosis</li> <li>• Intussusception</li> <li>• Necrotizing enterocolitis</li> <li>• Volvulus</li> </ul>
Other <ul style="list-style-type: none"> <li>• Child abuse</li> <li>• Severe anemia</li> <li>• Methemoglobinemia</li> <li>• Infant botulism</li> </ul>

## ***Pathophysiology and Long-term Outcome***

Neonatal diabetes mellitus (NDM) is a monogenic form of diabetes that occurs within the first 6 months after birth. It is a rare disorder, with an estimated incidence of 1 in 400,000 live births.<sup>1</sup> Infants who have NDM do not produce sufficient insulin, leading to an increase in blood glucose concentrations. In approximately 50% of those who have NDM, the condition is lifelong and is termed permanent neonatal diabetes mellitus (PNDM). In the remainder of affected infants, the condition is transient and disappears during infancy, although it can reappear later in life. This form is termed transient neonatal diabetes mellitus (TNDM).<sup>2</sup>

The cause of NDM is unclear, and its pathogenesis differs from that of insulin-dependent diabetes mellitus (IDDM) in childhood because of its highly variable course. The presence of islet cell antibodies has not been reported in NDM. The absence of autoimmune markers typical for IDDM also is consistent with the diagnosis.<sup>1</sup> C-peptide concentrations usually are low or undetectable because of impaired endogenous insulin secretion. Newborns who have NDM typically are small for gestational age, possibly because of the failure of insulin secretion in fetal life.<sup>3</sup>

The major cause of TNDM is aberrant expression of imprinted genes at chromosome 6q24.<sup>2</sup> There also have been reports of paternal isodisomy of chromosome 6 (the chromosome pair consists of two copies of the same paternal chromosome instead of following the normal pattern of biparental inheritance).<sup>4</sup> Transient neonatal diabetes mellitus usually presents within the first 8 weeks after birth with failure to thrive, hyperglycemia, and dehydration. There is evidence for failure of insulin production in response to glucose feeding, and insulin therapy is required. The condition typically lasts for weeks to months. Although affected children often have a permanent remission, they must be followed closely because there is a predisposition toward type 2 (insulin-resistant) diabetes later in life.<sup>5</sup>

Permanent neonatal diabetes mellitus usually is due to pancreatic aplasia, a congenital absence of the islets, or selective agenesis of beta cells.<sup>1</sup> Permanent neonatal diabetes mellitus is more likely to be associated with other abnormalities, including hypothyroidism, sensorineural deafness, cataracts, macroglossia, and hernias.<sup>5</sup> In one study examining NDM, 50% of the patients developed permanent diabetes.<sup>1</sup>

### ***Lessons for the Clinician***

Neonatal diabetes mellitus is a rare but serious condition that should be considered in the differential diagnosis of the ill-appearing infant. Close blood glucose monitoring is essential as long as hyperglycemia persists. Insulin therapy usually is required, but not always as a lifelong therapy. Because recurrent diabetes is common in patients who have TNDM, prolonged follow-up is imperative.

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Identifiable genetic mutations associated with NDM are attributable to methylation defects in 4 genes (*KCNJ11*, *ABCC8*, *6q24*, and *INS*). Although these defects lead to *impaired* insulin secretion, mutations of *KCNJ11* or *ABCC8* have been shown to lead to *excessive* insulin production (ie, persistent hyperinsulinemic hypoglycemia of infancy), which is described in Case 13. Genetic analysis is helpful to target treatment of NDM because if there are methylation defects in *KCNJ11* or *ABCC8*, treatment with sulfonylurea is more effective at achieving glycemic control compared with insulin.<sup>1,2</sup>

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## Premature Baby Girl With Ambiguous Genitalia

### Presentation

A 53-day-old, 27-weeks'-gestation female infant presents with genitalia that have become more noticeably ambiguous over the preceding several weeks (Figure 15.1).



**Figure 15.1.** Genitalia in a 53-day-old preterm infant.

### *Prenatal and Birth Histories*

Born to a 21-year-old G2P0010 (now G2P0111) mother.

Estimated gestational age at birth: 27 4/7 weeks.

Delivered via cesarean delivery due to severe maternal preeclampsia.

Mother on magnesium sulfate before delivery.

Pregnancy also complicated by maternal substance use and intrauterine growth restriction.

### ***Prenatal Laboratory Results***

Blood type: O+

Antibody screen: negative

Hepatitis B surface antigen: negative

HIV: negative

Rubella: immune

Gonococcus/Chlamydia trachomatis: negative

Rapid plasma reagin: unknown

Group B Streptococcus: unknown

### ***Resuscitation***

Apgar scores of 2, 5, and 7 at 1, 5, and 10 minutes, respectively.

Given positive pressure ventilation for 1 minute, bringing the heart rate from undetectable to 70s.

Intubated at 90 seconds. Heart rate above 100 after several minutes of ventilation.

Umbilical arterial catheter and umbilical venous catheter lines placed.

Surfactant given at 20 minutes after birth.

## **The Case**

Complicated neonatal intensive care unit course to date, which included the following:

Respiratory distress syndrome requiring surfactant  $\times 4$ .

Pulmonary hemorrhage.

Stints on high-frequency oscillator and conventional ventilator.

Intermittent apnea/bradycardia spells, treated with caffeine.

Grade II intraventricular hemorrhage diagnosed in first week after birth.

Bilateral retinopathy of prematurity.

Anemia and thrombocytopenia requiring several transfusions.

Repeat evaluations for necrotizing enterocolitis requiring setbacks in tube feeding.

Intermittent feeding intolerance and coffee ground residuals.

Direct hyperbilirubinemia presumed secondary to total parenteral nutrition cholestasis.

Intravenous antibiotic course for treatment of staphylococcal neck abscess.

## ***Case Progression***

### ***Vital Signs***

Temperature: 37.4°C

Heart rate: 157 beats/min

Respiratory rate: 55 breaths/min

Blood pressure: 77/48 mm Hg

Oxygen saturation: 97% on 2 L/min of 21% fraction of inspired oxygen

Weight: 1.4 kg (less than 3rd for % of age)

Length: 36 cm (less than 3rd for % of age)

Head circumference: 26.5 cm (less than 3rd for % of age)

### ***Physical Examination***

General: Small premature infant with limited subcutaneous fat. Awake and alert on examination.

Skin: Pink and warm throughout. No rashes, lesions, jaundice, petechiae, or birthmarks.

Head, Neck, Eyes, Ears, Nose, and Throat: Anterior fontanelle open, soft, and flat. No apparent dysmorphism aside from mildly downward-slanting palpebral fissures. Nares patent. Intact palate. Ears normal and symmetric in shape and position.

Respiratory: Breath sounds equal and clear bilaterally. No wheeze, crackles, or rhonchi. Normal work of breathing without distress.

Cardiovascular: Quiet precordium, normal S1 and S2, regular rate and rhythm, and no murmur. Capillary refill less than 3 seconds, pulses 2+ bilaterally in upper and lower extremities.

Abdomen: Soft, rounded, and nontender. No palpable mass or hepatosplenomegaly. Normal bowel tones.

Genitourinary: Mild to moderate clitoromegaly and firm, enlarged labia majora. Right labium particularly firm with possibility of small mass. Normal labia minora and urethral opening. Anus appears normal and patent.

Musculoskeletal: Extremities well formed with full range of motion. Back without defect. Hips without click or clunk.

Neurologic: Symmetric and spontaneous movements of all extremities. Normal neuromuscular tone and behavior for gestational age. Suck reflex intact.

### ***Laboratory Studies at 52 Days After Birth***

Sodium: 141 mmol/L

Potassium: 3.6 mmol/L

Chloride: 110 mmol/L

Bicarbonate: 23 mmol/L

Blood urea nitrogen: 5 mg/dL

Creatinine: 0.29 mg/dL

Glucose: 78 mg/dL

Calcium: 8.6 mg/dL

Magnesium: 2.6 mg/dL

Phosphorous: 5.7 mg/dL

Aspartate aminotransferase: 100 U/L

Alanine aminotransferase: 41 U/L

Alkaline phosphatase: 368 U/L

Total bilirubin: 4.5 mg/dL

Direct bilirubin: 3.7 mg/dL

Total protein: 3.2 g/dL

Albumin: 1.9 g/dL

Newborn screens: Normal except low T4 on first two, which normalized on third.

***Case Progression***

Endocrinology was consulted and recommended karyotype as well as pelvic and labial ultrasound to assess for a uterus and for intrapelvic or intralabial gonads. Karyotype returned as 46XX, and ultrasound revealed a uterus and bilateral pelvic gonads. Of note, the right gonad measured  $1.8 \times 1.2 \times 1.4$  cm and had several visible follicles, while the left measured  $0.8 \times 0.5 \times 0.3$  cm with a single tiny follicle. No gonads or other masses were visualized in the labia. Patient's clinical status deteriorated with onset of sepsis, and when baseline cortisol levels returned low at 2.8 and 4.2 mcg/dL (repeated 2 days apart), the decision was made to treat empirically with hydrocortisone. After clinical stabilization, steroids were tapered off, and 2 weeks later more extensive testing was performed with a corticotropin stimulation test and poststimulation levels of multiple hormones.

***Precorticotropin Stimulation at 93 Days After Birth***

Cortisol: 4.2 mcg/dL

***Postcorticotropin Stimulation at 93 Days After Birth***

Cortisol: 56.3 mcg/dL

17-hydroxy progesterone: 233 ng/dL

11-deoxycortisol: 69 ng/dL

Dehydroepiandrosterone (DHEA): 1,280 ng/dL

DHEA-S: 54 mcg/dL

Testosterone: 58 ng/dL

Estradiol: 107 pg/mL

***Laboratory Values Obtained at 100 Days After birth***

Follicle-stimulating hormone (FSH): 8.5 mIU/mL (normal infant, 0.24–14.2; normal prepubertal child, 1.0–4.2)

Luteinizing hormone (LH): 8.6 mIU/mL (normal infant, 0.02–7.0; normal prepubertal child, 0.02–0.3)

***Laboratory Values Obtained at 117 Days After Birth***

Testosterone: 58 ng/dL



## Differential Diagnosis

### *Ambiguous Genitalia in an Infant With 46XX Karyotype, a Uterus, and Pelvic Gonads*

Androgen excess due to congenital adrenal hyperplasia (CAH)

21 $\alpha$ -hydroxylase deficiency (95% of CAH)

Other enzymatic deficiencies (eg, 11 $\beta$ -hydroxylase, 17 $\alpha$ -hydroxylase, 3 $\beta$ -hydroxysteroid dehydrogenase, or oxidoreductase)

Androgen excess of non-CAH etiology (eg, aromatase deficiency)

Primary maternal virilizing process (eg, luteoma of pregnancy)

Abnormal ovarian development (eg, ovotesticular disorder of sex development)

*Take a moment to consider the diagnosis in this infant.*

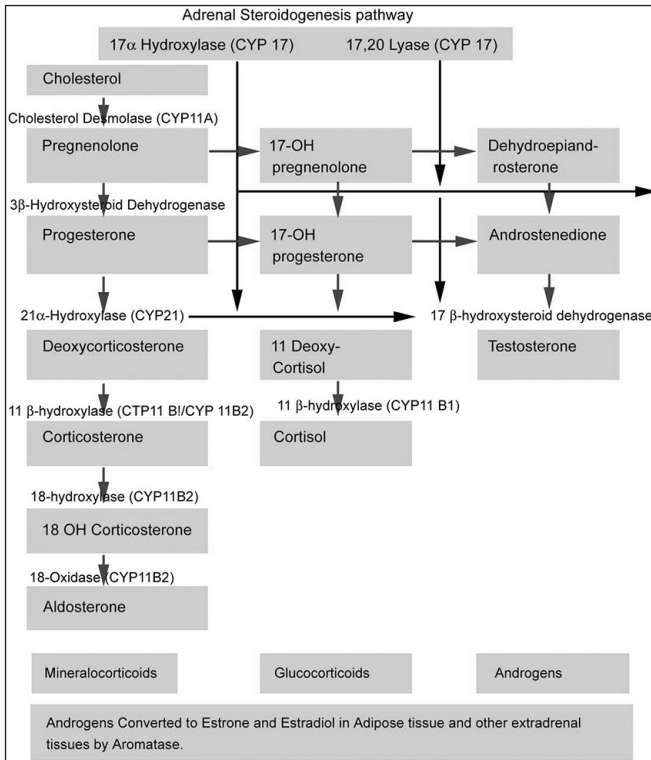
## Actual Diagnosis

### *Ovotesticular Disorder of Sex Development vs Oxidoreductase Deficiency*

The laboratory and imaging data in this case allowed for systematic narrowing of the differential diagnosis, although the specific defect at work has not been definitively established. We began with ambiguous genitalia, which could represent an undervirilized male infant, a virilized female infant, or an infant with a sex chromosome disorder of sex development (DSD), such as 45X/46XY mixed gonadal dysgenesis, or 46XX/46XY mosaicism. Obtaining the karyotype narrowed our possibilities to 46XX DSDs.

By far the most common cause of excess androgen production and resultant virilization in female infants is CAH due to 21 $\alpha$ -hydroxylase deficiency. However, three normal newborn screens and a normal 17-hydroxyprogesterone level after corticotropin stimulation ruled out this possibility for the infant in question. Results of the corticotropin stimulation test also allowed us to evaluate other enzymatic defects that could cause CAH. The normal stimulated cortisol level and lack of elevated precursors in the adrenal steroid synthesis pathway indicated that this infant did not have deficiency of 11 $\beta$ -hydroxylase, 17 $\alpha$ -hydroxylase, or 3 $\beta$ -hydroxysteroid dehydrogenase (see Figure 15.2, Uwaifo, 2011).<sup>1</sup>

Oxidoreductase deficiency can affect several of the enzymes in the steroid synthesis pathway to varying degrees and cause a wide variety of phenotypes involving virilization and skeletal abnormalities. Our infant did not have the skeletal abnormalities, modest elevation in 17-hydroxyprogesterone, or low cortisol in response to corticotropin that are most commonly seen in oxidoreductase deficiency. However, she could fall into a category of infants with oxidoreductase deficiency who do not exhibit these traditional characteristics on exam or laboratory testing (see Krone, 2012).<sup>2</sup>



**Figure 15.2.** Adrenal steroidogenesis pathway. Image reprinted with permission from Medscape Reference, 2013, available at: <http://emedicine.medscape.com/article/117012-overview>.

Our infant's laboratory results were notable for a high-normal DHEA at 1,280 (normal values of 67–1,453 ng/dL), a high testosterone at 58 (normal values of 2–8 ng/dL), and a high estradiol at 107 (50 pg/mL as upper limit of normal) for her gender and age group. These values, along with her elevated LH at 8.6 (normal values of 0.02–7 mIU/mL) and high-normal FSH at 8.5 (normal values of 0.24–14.2 mIU/mL) for age, indicated that sex hormone production was under the stimulus of pituitary LH and FSH. Furthermore, this infant's highly elevated testosterone level in relation to her estradiol level indicated that in her case the mini puberty of infancy was leading to excessive androgen production and likely causing the progressive virilization of her genitalia that had been observed by her medical providers.

The question of what defect led to excessive androgen production as compared with estradiol production in this infant remains uncertain. One possibility would be a defect or deficiency in the enzyme aromatase, which allows for conversion of

androgens to estradiol in peripheral tissues. However, fetal-placental aromatase deficiency typically leads to virilization of the mother during pregnancy, which was not definitively observed in this case. In addition, because this infant could synthesize some estrogen, she would have to suffer from only a partial deficiency or dysfunction of the enzyme, and it is unlikely that she would be able to produce an estradiol level as high as 107 pg/mL with such a defect.

Another possibility would be an ovarian or adrenal tumor, but her imaging was not consistent with such a mass. Ovotesticular DSD seems to be the most plausible diagnosis, supported by the asymmetry of her gonads on ultrasound (the left being significantly smaller and without normally numbered or sized follicles) and the persistent elevation of her testosterone during the mini puberty of infancy. However, an atypical oxidoreductase deficiency also has not been completely ruled out.

To determine the specific defect at work in this case, the medical team will repeat androgen, estradiol, FSH, and LH measurements at later time points to determine how these levels and ratios change as the infant winds down from her mini puberty of infancy. Measurement of anti-Müllerian hormone (AMH), a sexually dimorphic hormone, will also be undertaken to attempt to determine if testicular tissue is present. Finally, genetic testing may be pursued for mutations associated with oxidoreductase deficiency, as well.

This case highlights the difficulty in pinning down a genetic or biochemical defect with certainty when traditional CAH is not the underlying mechanism of virilization. If further testing does not lead to a certain diagnosis, this patient may still be followed clinically with the reassurance that she does not require glucocorticoid or mineralocorticoid replacement, but that she may require further intervention surrounding entry into puberty.

## The Experts

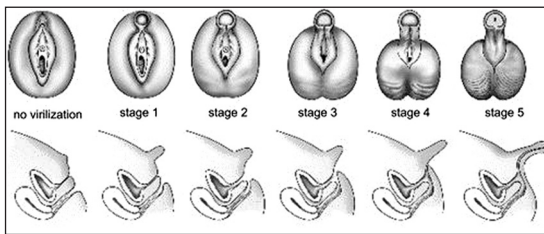
Approximately 1 in every 4,500 newborns will present with ambiguous genitalia. Uncertainty regarding the infant's gender is often disconcerting for parents and other family members. Therefore, a multidisciplinary team should be involved early on, including endocrinology, urology, neonatology, social work, psychology or psychiatry, and potentially genetics, to assist with an efficient diagnostic evaluation and decision about gender of rearing.

Our understanding of the genetic underpinnings for many root causes of DSDs has expanded greatly in the last 10 years. This has led to more detailed subdivisions within DSD categories and more nuanced understanding of the interaction between genetic defects and phenotypic expression in the individual. We now see that infants who have identical biochemical insults can manifest anywhere along a spectrum of physical abnormalities, likely determined by a host of cellular and molecular

variables that have yet to be fully characterized. This type of individual variability makes a systematic and thorough diagnostic evaluation essential to the proper identification and treatment of any infant who has ambiguous genitalia.

As with any medical condition, the evaluation process should begin with a careful history and physical examination. Particularly important are details such as maternal medication use during pregnancy (including any exogenous hormones taken for contraception or reproductive assistance), and any signs or symptoms of maternal virilization. Prenatal ultrasound results may be useful if genitalia were visualized, and genetic or chromosomal testing performed via amniocentesis should also be documented. Family history should focus on instances of known genitourinary defects, amenorrhea, infertility or frequent miscarriages, precocious or delayed puberty, neonatal demise, and consanguinity.

Physical examination should characterize the degree of virilization and can make use of the Prader scale, which comprises stages 1 to 5, as seen below (see Figure 15.3).<sup>3</sup>



**Figure 15.3.** Image reprinted with permission from Medscape Reference, 2013.

Along with staging of virilization, the genitourinary examination should focus on size of typical structures (measurements can be helpful), as well as presence and position of orifices. The examiner should also specifically note any palpable gonads, whether in the labioscrotal folds, in the inguinal canal, or in a superficial pelvic/abdominal location where they can be palpated. A palpable gonad typically represents either a testis or an ovotestis and can significantly narrow the differential diagnosis. A thorough examination for other dysmorphisms or congenital malformations, overall degree of prematurity, and general clinical status is also key, and review of vital signs and laboratory results is essential to evaluate for potential side effects of CAH, such as hypertension and salt wasting.

Next steps in the diagnostic evaluation should include a karyotype and imaging of the genitourinary system, which is most often done via ultrasound. After determination of sex chromosomes and Mullerian versus Wolfian structures, further testing will depend on these initial results, although it will often include hormone levels such as were assessed in our case. One important point when performing hormone assays is to employ a laboratory that specializes in these tests and can provide more accurate and precise reference ranges for infants, rather than measuring results

against adult norms. All laboratory and imaging data should be interpreted by a specialized and multidisciplinary team so that the proper diagnosis can be made and appropriate treatment and prognosis explained to the family.

*Stephanie S. Crossen, MD, MPH, Cheryl Hanna, MD, JoDee M. Anderson, MD, MEd, Oregon Health & Science University, Portland, OR*

### **FOLLOW-UP COMMENTARY BY DR CHERYL HANNA**

Follow-up of this infant has been ongoing. No definite diagnosis has been identified.

At 6 months chronological age, the infant's testosterone had decreased to 9 ng/dl. Both LH and FSH levels were in the prepubertal range. The infant's AMH was measured at age 6 and 9 months and values were normal for a female infant. At 9 months of age, the infant's pelvic ultrasound showed two normal-sized ovaries.

The infant's exam at age 9 months showed that the virilization was resolved (as the baby grew bigger, the clitoris did not continue to enlarge). The infant's linear growth and weight gain have been normal.

Assessment: Ovotesticular DSD is less likely (no evidence for testicular tissue).

Oxidoreductase deficiency now seems to be the most likely diagnosis. The plan is to reevaluate as the child nears puberty.

## **Hypoglycemia in a Term Appropriate-for-Gestational-Age Infant**

### **Presentation**

A term male infant is transferred to the neonatal intensive care unit for persistent hypoglycemia at age 3.5 hours. The infant had a blood sugar level of 21 mg/dL at age 3 hours, and despite refeeding 20 mL of 20 calories per ounce of formula, his blood glucose level remained at 20 mg/dL at 3.5 hours.

The infant was born via cesarean delivery for a nonreassuring heart rate tracing to a 19-year-old G1P0 African-American mother. All prenatal laboratory results were negative, including an oral glucose tolerance test. Prenatal ultrasonography was performed during the second trimester and showed no gross fetal anomalies other than the presence of a two-vessel cord.

The infant cried spontaneously at birth and had some transient respiratory distress. The infant weighs 2,960 g (50th percentile) with a length of 48 cm (50th percentile) and a head circumference of 32.5 cm (25th–50th percentile). Results of the physical examination are normal except for a small penis (stretched penile length of 1.5 cm, width of 0.6 cm) and an undescended left testicle. Blood glucose levels below 40 mg/dL persist despite 2 boluses of 10% dextrose and administration of continuous dextrose infusion with a glucose infusion rate of ~5 mg/kg per minute. Glucose levels above 40 mg/dL are eventually achieved with a glucose infusion rate of 8 mg/kg per minute.

The pediatric endocrinology service was consulted on the second day for persistent hypoglycemia.

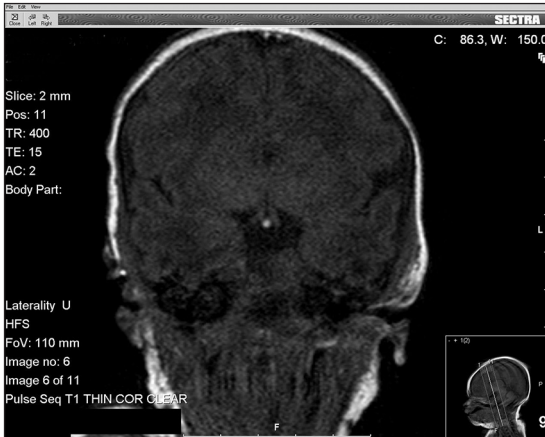
## Discussion

The differential diagnosis of hypoglycemia in the newborn is very broad and includes prematurity, intrauterine growth retardation, infant of a diabetic mother, hypothermia, perinatal asphyxia, and sepsis. These entities were quickly ruled out given the negative history and physical examination. Disorders of gluconeogenesis/ glycogenolysis, hyperinsulinism, and primary and secondary adrenal insufficiency were then considered, especially in the context of the physical finding of a micropenis.

Common causes of micropenis (microphallus) in a newborn include hypogonadotropic hypogonadism from pituitary and hypothalamic lesions, hypergonadotropic hypogonadism (primary testicular failure), septo-optic dysplasia sequence, Smith-Lemli-Opitz syndrome, Kallmann syndrome, and Prader-Willi syndrome. Micropenis is often associated with major chromosomal defects, including Klinefelter syndrome (47,XXY) as well as other X polysomy syndromes and translocations, deletions, and trisomy involving chromosomes 8, 13, and 18. An apparent micropenis could also result from the virilization of the female external genitalia in cases of congenital adrenal hyperplasia due to 21 $\alpha$ -hydroxylase and 11 $\beta$ -hydroxylase deficiency.

A pelvic and renal ultrasound is performed on day 2 due to the presence of the two-vessel cord as well as the undescended testicle. No evidence of hydronephrosis or other renal malformations is found. The pelvic ultrasound confirms the bilateral presence of testes in the inguinal canal and the absence of a uterine cavity. At age 60 hours, the infant is noted to have an elevated serum bilirubin level of 13.0/0.3 mg/dL, and treatment with phototherapy is begun. Hyperbilirubinemia resolves by age 90 hours.

A magnetic resonance imaging (MRI) study of the brain is performed without intravenous contrast. Axial and sagittal T1-weighted, transaxial T2-weighted, transaxial fluid-attenuated inversion recovery, and echo-planar diffusion-weighted pulse sequences are done. Ectopic location of the pituitary bright spot is seen in the region of the hypothalamus, signifying an ectopic posterior pituitary (Figure 16.1). The pituitary infundibulum is not identified. No mass effect or midline shift is noted.



**Figure 16.1.** Magnetic resonance imaging demonstrating pituitary bright spot and absence of pituitary infundibulum.

### Laboratory Findings

Endocrine laboratory results on day 2 are shown in Table 16.1.

**Table 16.1.** Chromosomal Analysis: 46,XY

Hormone	Reference Value	Results
Cortisol	1.7–14 $\mu\text{g/dL}$	0.14 $\mu\text{g/dL}$
Adrenocorticotrophic hormone	7.2–63.3 pg/ml	<5 pg/mL
Free T4	8.2–19.9 ng/dl	0.71 ng/dL
Thyroid-stimulating hormone	0.7–15.2 IU/L	8.53 mIU/L
Growth hormone (random)	5–53 ng/ml	3.2 ng/ml
Insulin growth factor-1	15–109 ng/ml	<16 ng/mL
17OH progesterone	7–77 ng/dL	19 ng/dL
Testosterone	75–400 ng/dL	13 ng/dL
Follicle-stimulating hormone	<0.2–0.8 mIU/mL	0.20 mIU/mL
Luteinizing hormone	0.02–7 mIU/mL	<0.07 mIU/mL

*Take a moment to consider the diagnosis in this infant.*



## Diagnosis

The diagnosis is congenital hypopituitarism.

## Pathophysiology

Hypopituitarism denotes underproduction, deficiency, or lack of secretion of more than 1 anterior pituitary hormone. The incidence of congenital hypopituitarism is thought to be between 1 in 4,000 and 1 in 10,000 live births. Defects in the genes that encode the transcription factors, such as *PROP1*, *POU1F1*, *LHX3*, *LHX4*, and *HESX1*, which are necessary for the differentiation of anterior pituitary cells, have recently been found to be responsible for the development of congenital hypopituitarism.<sup>1</sup> The likelihood of finding mutations is increased by a positive family history, with gene mutations found in 13% of isolated growth hormone (GH) deficiency and 20% of multiple pituitary hormone deficiency cases.

The clinical manifestations of hypopituitarism depend on which anterior pituitary hormones are deficient. Severe prenatal deficiency of GH, as occurs in congenital hypopituitarism, has little effect on fetal growth because in utero growth is dependent on insulin, insulin growth factor-1 (IGF-1), and insulin growth factor-2. It does, however, present as micropenis, especially when gonadotropins are also deficient. In addition to micropenis in males, additional consequences of severe GH deficiency in the first days after birth may include hypoglycemia and exaggerated jaundice (both direct and indirect hyperbilirubinemia). Symptoms of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency in a newborn male can also cause micropenis, testicular hypofunction, and undescended testis. LH in utero is important for the stimulation of the LH/choriogonadotropin receptor, which leads to testosterone synthesis in the Leydig cells and plays an important role in the descent of the testes. Gonadotropin deficiency in males subsequently leads to testosterone deficiency, infertility, and osteopenia/osteoporosis. In females, there are no obvious manifestations of gonadotropin deficiency in the neonatal period, but eventually in adolescents, it leads to failure of pubertal development, primary amenorrhea, and infertility.

The presentation of adrenocorticotrophic hormone (ACTH) deficiency is almost exclusively related to glucocorticoid (cortisol) deficiency resulting in hypoglycemia. Of note is that ACTH deficiency does not cause salt wasting and hyperkalemia because it does not result in deficiency of aldosterone. The clinical manifestations of thyroid-stimulating hormone (TSH) deficiency are similar to those of primary hypothyroidism. Large fontanelles, lethargy, constipation, hoarse cry, hypotonia, hypothermia, and jaundice are known to occur if thyroid replacement therapy is not promptly started. Symptoms usually develop within the first 2 weeks and are almost always present by 6 weeks.

The diagnosis of panhypopituitarism is the sum of the clinical findings of micropenis, undescended testis, persistent hypoglycemia, and prolonged jaundice, along with laboratory evaluation of each pituitary hormonal axis, such as ACTH–cortisol; TSH–free T4; GH–IGF-1; LH & FSH–testosterone, and an MRI of the pituitary gland. The review of the endocrine laboratory values in this case shows low concentrations of cortisol and undetectable levels of ACTH. Free T4 levels are also low, which is consistent with central hypothyroidism. The TSH concentrations are generally low but sometimes can be in the normal range, as in our case. The IGF-1 levels were undetectable. Unstimulated GH levels are not useful for the diagnosis of GH deficiency, but the undetectable levels of IGF-1 are consistent with GH deficiency. The gonadotrophins, LH and FSH, start to rise to pubertal levels at age 2 weeks as part of a postnatal surge. Luteinizing hormone and FSH levels, which were repeated at 2 weeks, were low; this finding is also consistent with gonadotropin deficiency. A formal evaluation of gonadotropin deficiency with a Lupron stimulation test will be done in the future.

The posterior pituitary seems to be functioning because serum sodium levels have remained normal and the pituitary bright spot is identified, consistent with the presence of arginine vasopressin–producing cells. The combination of anterior pituitary hormone deficiencies along with the MRI finding of an ectopic posterior pituitary points toward a defect in one of the transcriptional factors necessary for pituitary development. Any such factor is yet to be investigated and identified in this patient. The investigation of genetic diagnosis is imperative in these cases; the family should undergo genetic counseling, and the first-degree family members should be analyzed for genetic mutations as well. If the mutation occurred *de novo* in this patient, then the chances of panhypopituitarism in another sibling are low compared with an autosomal recessive or autosomal dominant trait. Patients who have transcription factor deficiency have also been reported to present with developmental, motor, and speech delays.

### ***Management and Long-term Outcome***

Treatment of panhypopituitarism involves the replacement of each deficient pituitary hormone. The patient may also require surgical correction of undescended testis along with human chorionic gonadotropin or short-term androgen treatment, which aids in the descent and improvement of micropenis. Some patients who have panhypopituitarism may also require early intervention services for physical, speech, and occupational therapy.

In our patient, hydrocortisone is started at a dose of 2.5 mg 3 times a day on day 2 due to low cortisol levels, which is later increased to 5 mg 3 times a day (supraphysiologic dose) due to the persistence of hypoglycemia. Levothyroxine (12.5 mcg orally daily) is started on day 3 for hypothyroidism secondary to a repeat low free T4 level. Growth hormone (0.1 mg subcutaneously daily [ie, 0.3 mg/kg per week]) is

started on day 4 due to low IGF-1 levels, the findings of micropenis, and the persistence of intermittent hypoglycemia despite a supraphysiologic dose of hydrocortisone. Before discharge, the patient's parents are taught how to use a glucometer and how to recognize the signs of adrenal insufficiency. The infant is discharged from the hospital with supplies of glucagon and Solu-Cortef® (Pfizer Inc., New York, NY) emergency kits. The parents are also instructed to increase the dose of hydrocortisone during periods of stress and fever. Gonadotropin and sex steroid replacement will be started at the time of initiation of puberty and adolescence.

### **Lessons for the Clinician**

Endocrine disorders may present in the neonatal period as persistent hypoglycemia.

Micropenis and undescended testes may be an important sign of GH and gonadotropin deficiency.

A thorough investigation of all pituitary hormones is indicated when any single deficiency is identified. These deficiencies are readily identified by using laboratory values.

*Mai Miyaji, MD, Nitya Gulati, MD, Gratiyas Mundakel, MD, Amrit Bhangoo, MD, and Ivan Hand, MD, Division of Neonatology, Department of Pediatrics, Kings County Hospital Center, SUNY–Downstate School of Medicine, Brooklyn, NY*

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## **Six-Day-Old With Tachycardia and Tachypnea**

### **Presentation**

A female infant presents with extreme tachycardia and tachypnea on the sixth day after birth. She was born at 35 1/7 weeks' gestation dated by the mother's last menstrual period and first trimester ultrasonography. The 26-year-old G1P0 mother has a history of anemia and fibroids. Prenatal laboratory results were AB+ blood type, syphilis screen-nonreactive, hepatitis B surface antigen-negative, HIV-negative, rubella-immune, and gonorrhea- and chlamydia-negative. Group B streptococcal culture was pending at delivery.

The mother presented in preterm labor several hours after rupture of membranes at home with clear amniotic fluid. The infant was delivered by cesarean section due to progressing preterm labor and a frank breech presentation. The infant initially had poor color, tone, heart rate, and respiratory effort, necessitating neonatal resuscitation. After 2 minutes of positive pressure ventilation, the infant stabilized. Apgar scores were 5 at 1 minute and 8 at 5 minutes after delivery. After resuscitation, the infant continued to have nasal flaring and increased work of breathing and was transferred to the neonatal intensive care unit (NICU) for further care.

### ***Initial Vital Signs***

Weight, 2,185 g (seventh percentile)

Length, 46 cm (30th percentile)

Head circumference, 32 cm (30th percentile)

Temperature, 36.6°C

Heart rate, 152 beats/min

Respiratory rate, 58 breaths/min

Blood pressure, 76/46 mm Hg

Oxygen saturation, 92% on room air

On physical examination, the infant had mild respiratory distress and a soft 2/6 systolic murmur over the apex, but other findings were normal. She was placed on oxygen via nasal cannula while an initial chest radiograph and blood gas were obtained. An intravenous catheter was placed, and infusion of a 10% dextrose solution at 60 mL/kg per day was started. A complete blood count and blood culture were obtained, and empiric antibiotic therapy with ampicillin and gentamicin for possible sepsis was initiated.

The infant's respiratory distress resolved by the second day after birth, and she was breathing room air comfortably. She worked on her ability to feed by mouth over the next several days without issue. The antibiotics were stopped after 48 hours because of no growth on the initial blood culture.

Over the course of her sixth day after birth, her heart rate increases to more than 220 beats/min, respiratory rate increases to more than 100 breaths/min, and she becomes irritable and agitated. A repeat chest radiograph shows an enlarged cardiothymic silhouette (Figure 17.1) with normal pulmonary vascular markings. Blood pressure and oxygen saturations are normal. A 12-lead electrocardiogram demonstrates sinus tachycardia with right ventricular hypertrophy that is normal for age.

Echocardiography reveals normal size, anatomy, and function of the heart. The infant has blood, urine, and cerebrospinal fluid specimens drawn for culture and is again started on broad-spectrum empiric antibiotics without improvement. Further history from the mother and a blood test from the infant reveal the diagnosis.



**Figure 17.1.** Repeat chest radiograph.

## Discussion

### ***Further History and Laboratory Results***

The mother, who spoke limited English and was difficult to understand, recalled being sent to a different doctor, who diagnosed her with a neck disorder during the pregnancy. She was started on a medication and had blood studies performed but was unsure of the results. She was not able to make her follow-up appointment with this physician but continued her regular prenatal care.

*Take a moment to consider the diagnosis in this infant.*

The woman had no proptosis or other overt clinical signs of hyperthyroidism. However, a review of her chart confirmed a diagnosis of Graves disease 2 months prior to delivery, when propylthiouracil (PTU) therapy was initiated. Her laboratory results at that time were

- Free thyroxine, >6 ng/dL (77.2 pmol/L) (normal, 0.7 to 1.48 ng/dL [9.0 to 19.0 pmol/L])
- Thyroid-stimulating hormone, 0.016 mIU/mL (normal, 0.35 to 4.94 mIU/mL)
- Thyroid-stimulating immunoglobulin, 307% (normal, <129%)

The infant's laboratory results were

- Free thyroxine, >6 ng/dL (77.2 pmol/L)
- TSH, <0.01 mIU/mL
- Thyroid-stimulating immunoglobulin, 286%

Such results confirm the diagnosis of neonatal thyrotoxicosis. Follow-up examination of the infant revealed no proptosis but a very small palpable goiter.

### ***Differential Diagnosis***

Tachycardia and tachypnea are seen frequently in the NICU and can present a diagnostic challenge because of multiple potential causes. Important diseases to consider in the initial evaluation include sepsis, meningitis, pneumonia, respiratory distress syndrome (RDS), pneumothorax, structural congenital heart disease, cardiomyopathies, and neonatal abstinence syndrome. Because the infant's symptoms were not present at birth and progressively worsened over time despite broad-spectrum antibiotic therapy, a bacterial infectious cause was less likely in this case. Pneumonia and RDS can worsen over time, although affected infants usually are symptomatic immediately from birth. The enlarged cardiomyopathic silhouette in this patient suggested heart disease but was ruled out with normal findings on echocardiography. The irritability, agitation, tachycardia, tachypnea, preterm birth, and low birthweight for gestational age in this patient were highly suggestive of neonatal thyrotoxicosis, which was confirmed with follow-up history and laboratory

investigation. Other symptoms often seen in infants who have hyperthyroidism are goiters, exophthalmos, hypertension, microcephaly, craniosynostosis, restlessness, diaphoresis, vomiting, diarrhea, hepatosplenomegaly, and poor weight gain.

### ***Pathophysiology/Incidence/Natural History***

Neonatal thyrotoxicosis is caused by the transfer of maternal thyroid antibodies across the placenta, which can occur as early as 20 weeks' gestation. Such immunoglobulin G antibodies come in two varieties: TSH-stimulating antibody (TSAb) and TSH-blocking antibody (TSBAb). Both can bind to the TSH receptor (TSH-R) on the surface of the infant's thyroid gland. When the TSAb binds to the TSH-R, the thyroid gland releases thyroxine (T4) and triiodothyronine (T3) as if stimulated by TSH itself, resulting in hyperthyroidism. Thyroid antibodies also occasionally can cross-react with the thymus, causing an enlarged cardiothymic silhouette on chest radiograph. Unfortunately, the thyroid antibodies do not participate in the negative feedback loop between the hypothalamus (thyrotropin-releasing hormone), the anterior pituitary (TSH), and the thyroid gland (T3/T4), so the thyroid gland remains hypersecretory until the antibody concentration decreases or is turned off/controlled by medication. Although the effect of TSBAb is antagonistic to TSAb, the concentrations of TSAb almost always are significantly higher and have a much longer half-life. Thyroid antibody concentrations decrease over time and usually dissipate by 8 to 20 weeks of age, although occasionally they are detectable until 6 months of age. Almost all infants who have neonatal thyrotoxicosis of this origin are euthyroid by 7 months.

Only 1% of pregnant women have thyroid disease, but 10% to 15% can have detectable thyroid antibodies. Women who have a history of thyroid disease requiring surgery or ablation can have detectable antibody many years later. Significant variability exists in the uptake and metabolism of thyroid antibody such that 1.5% to 12% of infants whose mothers have Graves disease develop clinical hyperthyroidism.<sup>1</sup> Furthermore, although variability exists in the literature regarding what maternal antibody value predicts which infants will be affected, most authors agree that the antibody concentrations should be monitored during pregnancy.<sup>2</sup> Unfortunately, the mortality rate from neonatal thyrotoxicosis can be as high as 25%.<sup>3</sup>

### ***Treatment***

The two primary goals of treating neonatal thyrotoxicosis are to minimize the symptoms of hyperthyroidism while attempting to achieve a euthyroid state. Infants who have no overt clinical signs and only a laboratory diagnosis usually can be observed closely without pharmacologic management. Infants who have obvious clinical compromise usually require a two-medication approach using a beta blocker for symptom control and an antithyroid agent to suppress thyroid hormone production. The antithyroid drug should be started at a low dose and titrated according to biweekly

to weekly free T4 and TSH values until the euthyroid state is maintained, after which time the laboratory assessment can be spaced out accordingly. Antithyroid agents such as methimazole, carbimazole, and PTU may require several days for full effect, requiring the most severely affected infants to undergo complete thyroid suppression with Lugol solution. With this approach, thyroid hormone replacement therapy with levothyroxine is used to achieve the euthyroid state. Occasionally, some infants require complete suppression along with replacement therapy.

This infant required symptomatic control with propranolol and complete thyroid suppression with PTU over several days. She was asymptomatic after 1 week of treatment, and the propranolol was discontinued. She was maintained on levothyroxine while assessing her antibody concentrations. Antibody no longer was detectable by 4 months of age, and she was slowly weaned off both the PTU and the levothyroxine by 6 months of age. When last seen at 12 months of age, she had normal growth and development and was euthyroid.

Why did this infant not manifest symptoms of hyperthyroidism at birth or even in utero, and why did symptoms not appear until 6 days after birth? The mother likely was euthyroid prior to delivery due to the PTU she was receiving. Because PTU crosses the placenta, the infant would have had an effective concentration at birth. As the PTU concentration began to fall in the infant, the antithyroid antibodies persisted, causing the infant to become progressively more hyperthyroid.

### **Lessons for the Clinician**

Neonatal thyrotoxicosis is rare but can be lethal if not diagnosed in a timely fashion. This case highlights the importance of good communication between the obstetrician or maternal fetal medicine specialist and the pediatrician or neonatologist. Pregnant women who have histories of Graves disease should have thyroid function studies and antibody concentrations assessed during pregnancy, and this information should be relayed to the pediatric service to allow appropriate observation and follow-up of the infant.

*John Podraza, MD, Department of Neonatology, National Naval Medical Center, Assistant Professor of Pediatrics, Uniformed Services University, Bethesda, MD.*

### **Acknowledgments**

The author would like to thank Dr Bill Scouten, pediatric endocrinologist, for his guidance with this case. Dr Podraza is a Lieutenant in the United States Navy. The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.



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### COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER

If the maternal diagnosis of Graves disease had been known prior to this infant's birth, the obstetric team could have measured maternal TSH receptor antibodies (TRAbs) during the second or third trimester. If a neonate is born to a woman with elevated TRAbs, TRAb levels should be obtained from the umbilical cord at the time of birth to identify neonates at risk for hyperthyroidism. High-risk neonates need to be followed for 2 to 3 months to assess for clinical and/or laboratory evidence of hyperthyroidism. Van der Kaay et al present a logical algorithm to monitor newborns born to women with Graves disease.<sup>1</sup>

1. Van der Kaay, DCM, Wasserman JD, Palmert MR. Management of neonates born to mothers with Graves' disease. *Pediatrics*. 2016;137:1–11

*Part 4*

# **Fluids and Electrolytes**

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## Hypernatremia in a 2-Week-Old Preterm Infant

### Presentation

A 2-week-old Hispanic male infant is admitted with a 1-day history of subjective fever, nonbilious vomiting, decreased oral intake, and lethargy. The physical examination is normal other than two small pustules, one on the cheek and the other on the scalp; both are sent for culture. He was born at 33 5/7 weeks' gestation to a 27-year-old G8P65116 woman. The mother had prenatal care starting at approximately 4 months of gestation that was complicated by premature and prolonged rupture of membranes (22 hours) with purulent amniotic fluid. Her laboratory evaluation included the following: blood group AB+, rapid plasma reagin nonreactive, hepatitis B negative, HIV negative, and urine drug screen negative. Her group B Streptococcus, chlamydia, gonorrhea, and rubella screens are unknown. The mother received azithromycin and metronidazole during labor and delivery. The infant was delivered via emergent cesarean delivery for chorioamnionitis. His Apgar scores were 4 and 8 at 1 and 5 minutes, respectively. The infant had neither a feeding problem nor apnea/bradycardia and received ampicillin and gentamicin intravenously for 7 days due to the maternal chorioamnionitis. His blood culture was negative. He was discharged home at 9 days of age.

When he arrives back at 2 weeks of age, a complete evaluation for neonatal sepsis is initiated, and herpes simplex virus (HSV) infection is suspected. He receives empiric treatment with acyclovir, vancomycin, and cefotaxime.

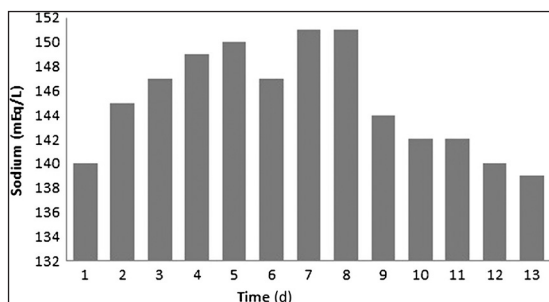
### Admission Laboratory Data

Complete blood count: white blood cell (WBC) counts 6,400/mm<sup>3</sup>; Hgb, 13.7 g/dL; Hct, 40.9%; and platelets, 409,000/mm<sup>3</sup>. White blood cell counts differential: segmented forms, 55%; bands, 4%; lymphocytes, 26%; and monocytes, 14%.

Urinalysis: specific gravity, 1.015; negative glucose, small amount of blood, trace protein, no WBCs/high power field, 0 to 2 red blood cells/high power field.

Cerebrospinal fluid (CSF): glucose, 34 mg/dL; protein greater than 460 mg/dL; red blood cell count, 26,200/mm<sup>3</sup>; WBC count, 100/mm<sup>3</sup> with neutrophils 5%, lymphocytes 94%, and monocyte 1%. The basic metabolic profile is as follows: sodium, 140 mEq/L; potassium, 5.1 mEq/L; chloride, 101 mEq/L; bicarbonate, 27 mEq/L; anion gap, 17.1 mEq/L; blood urea nitrate, 20 mg/dL; and creatinine, 0.4 mg/dL.

His weight at birth and this admission are 2.47 kg and 2.6 kg, respectively. The infant's hospital course is notable for a few days of hypothermia, good formula feeds, normal voiding and stooling, and adequate weight gain. Both the vesicular lesions and the CSF results are positive for HSV, and he completes a course of acyclovir. Hypernatremia is noted in serial blood draws (Figure 18.1).



**Figure 18.1.** Daily serum sodium.

## Discussion

The etiology of hypernatremia ( $\text{Na} > 150 \text{ mEq/L}$ ) in this case can be multifactorial. Preterm infants and newborns have decreased capacity to handle water and solutes, a physiologic feature that improves with age; our infant was born prematurely at 33 5/7 weeks. Once glomeruli are fully formed by 34 weeks, the glomerular filtration rate (GFR) begins increasing until birth, doubles by 2 weeks of age, and reaches adult levels by 1 year of age.<sup>1</sup> Our patient had a normal estimated GFR of 48 mL/min per 1.73 m<sup>2</sup> body surface area as determined by the Schwartz equation ( $\text{GFR} = [0.41 \times \text{height in cm}] / \text{creatinine in mg/dL}$ ). He is receiving premixed formula in the hospital, thus precluding improper formula mixing or exclusive breastfeeding as etiologies for hypernatremic dehydration. He has normal urine output and a normal specific gravity, and we have no suspicion for increased water loss from excessive insensible loss (extreme premature infants are at risk) as he is wearing a head cap, is swaddled, and is in normal room temperature. He has no diarrhea, no evidence of diabetes insipidus (possible with meningitis/encephalitis, but our infant is not so sick as to suggest this), and no evidence of renal dysplasia or obstructive uropathy. Blood and albumin infusion can increase serum sodium, but he is receiving neither. A search for exogenous sources of sodium (sodium bicarbonate, sodium chloride infusions) or primary hyperaldosteronism is initiated. This infant is hyperchloremic

and hypernatremic without metabolic acidosis (metabolic acidosis typically seen with multiple normal saline boluses). A review of his fluids received since admission reveals only dextrose 5% with 0.25% normal saline and maintenance potassium as IV fluids for few hours on the third day of hospitalization while awaiting his brain magnetic resonance imaging.

*Take a moment to consider the diagnosis in this infant.*

Our clinical pharmacist calculates the sodium intake from normal saline flushes and antibiotics as sodium salts. To our surprise sodium intake from these (hidden) sources is 9 mEq/kg per day. Combined with the daily sodium from his formula, the additional sodium is an excess load on his premature kidneys. Hypernatremia improves with reducing his medications to acyclovir, mixing his antiviral with 5% dextrose, and infusing a minimum volume of saline flushes (ie, we switch from pediatric to neonatal policy on IV flushes).

Hypernatremia is a common and usually preventable problem. Exclusively breastfed infants are at risk, and it can be generally prevented by measures such as ensuring adequate breastfeeding and weighing with close follow-up. Cases of hypernatremia secondary to the practice of salting the infant's skin have been reported.<sup>2</sup> Diarrhea with excess water loss is a common cause of hypernatremia in infants younger than 12 months. A case report similar to this case has been published on radial artery heparinized saline infusion causing hypernatremia.<sup>3</sup> Maintaining homeostasis in these infants is important because hypernatremia is associated with high osmolality resulting in cerebral vein thrombosis, intracranial hemorrhage, cerebral edema, and death.<sup>4,5</sup> Management of hypernatremia involves treating the underlying cause, removing excess sodium, and providing appropriate free water intake.<sup>6</sup>

### **Lessons for the Clinician**

Fluid and electrolytes are well managed in the neonatal intensive care unit on a daily basis. As a practitioner on a general pediatric ward, one must take the lessons learned from the neonatal area and be cautious using excess sodium and fluids in these small infants with renal immaturity who have challenges in handling sodium and water. Using small-volume IV flushes, avoiding unnecessary IV maintenance fluids in a well-feeding infant, eliminating insensible water loss, and using nephrotoxic drugs and contrast materials for imaging judiciously can help prevent hypernatremia.

*Anand Gourishankar, MD, Robert Yetman, MD, Division of Community and General Pediatrics, UT Medical School at Houston, TX.*

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### COMMENTARY BY DR JOSEF NEU, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE

This case demonstrates that use of IV flushes and certain medications may provide hidden sources of sodium to susceptible neonates. It would have been of greater interest if the actual intakes had been more specifically described. Nevertheless, the message is clear that when we observe hypernatremia, a careful accounting of intakes can be very helpful in establishing the diagnosis and providing treatment.

*Part 5*

# **Gastroenterology**



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## **Poor Feeding and Emesis in a 1-Day-Old Boy**

### **The Case**

A 1-day-old term male infant presents with poor feeding and emesis.

### ***Prenatal History***

21-year-old gravida 4 para 0030 Hispanic mother

Estimated gestational age: 38 weeks

Blood type A+, rapid plasma reagin nonreactive, hepatitis B surface antigen negative, rubella immune, group B Streptococcus (GBS) screen positive

Cesarean section delivery for possible active herpes simplex virus (HSV) lesion on the labia; mother had been treated with valacyclovir 3 weeks prior to delivery

Spontaneous rupture of membranes 1 hour prior to delivery; clear fluid

One dose of penicillin given for GBS prophylaxis

### ***Birth History***

The infant was delivered in vertex presentation by cesarean section. He was vigorous at birth, with a spontaneous cry. Apgar scores were 9 at 1 minute and 9 at 5 minutes. He initially went to the normal newborn nursery and breastfed. His birthweight was 3,220 g, which was appropriate for gestational age.

## Presentation

The infant continued to breastfeed well during the first day after birth. He had two wet diapers. At nearly 24 hours after birth, he had not yet passed meconium, and a glycerin suppository was administered, with resulting passage of meconium. At 36 hours of age, the patient appeared sleepy and not interested in feeding. There was one large mucus-filled emesis after a feeding.

## Case Progression

### *Vital Signs*

Heart rate: 104 beats/min

Respiratory rate: 60 breaths/min

Blood pressure: 88/54 mm Hg

Temperature: 37°C (98.6°F)

### *Physical Examination*

No dysmorphic features; intact palate

Lungs: Clear; equal breath sounds

Cardiovascular Examination: Normal S1, S2; regular rhythm; no murmur; equal peripheral pulses

Abdomen: Distended and firm; mild tenderness is elicited; bowel sounds are diminished; no discoloration

Genitourinary Examination: Normal male; testes are in the scrotum bilaterally and appear normal

Extremities: Normal; hips stable

Neurologic Examination: Appropriate strength and tone; quiet generally, with normal cry when handled

Skin: Mild icterus

Complete blood count (CBC), blood culture, and cerebrospinal fluid studies are sent for evaluation of sepsis, along with studies for HSV. The patient is started on ampicillin, gentamicin, and acyclovir. An abdominal radiograph (Figure 19.1) demonstrates markedly dilated bowel loops, although normal-caliber small bowel loops also are seen.



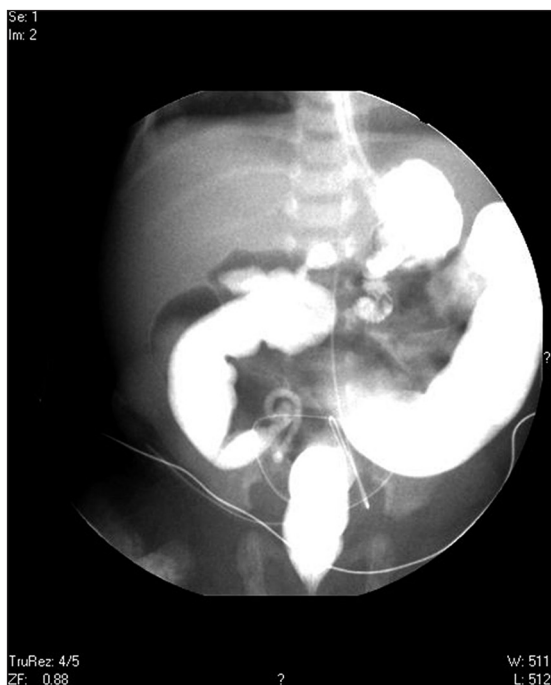
**Figure 19.1.** An abdominal radiograph demonstrates markedly dilated bowel loops, although normal-caliber small bowel loops also are seen.

The evaluation for sepsis appears negative. An orogastric tube is placed for suctioning, and surgical consultation is obtained.

A colon enema contrast study (Figure 19.2) does not reveal a transition zone. A moderate amount of meconium is expelled during the study. The distended bowel loops all fill with contrast during the study, suggesting that most of the distension is occurring in the large bowel. Although distended, the loops appear to be of normal caliber.



**Figure 19.2.** A colon enema contrast study does not reveal a transition zone. A moderate amount of meconium is expelled during the study. The distended bowel loops all fill with contrast during the study, suggesting that most of the distension is occurring in the large bowel. Although distended, the loops appear to be of normal caliber.



**Figure 19.3.** An upper gastrointestinal contrast study is conducted with small bowel follow-through. In this image, residual contrast from the enema study is seen.

An upper gastrointestinal contrast study is conducted with small bowel follow-through. In this image, residual contrast from the enema study is seen (Figure 19.3).

Results of the upper gastrointestinal study are normal, with a normal duodenal jejunal junction seen.

### ***Differential Diagnosis***

#### ***Term Infant Presenting at 36 Hours After Birth With Lethargy, Emesis, and Abdominal Distension***

Duodenal atresia

Gastroesophageal reflux

Group B streptococcal sepsis

Herpes simplex virus infection

Hirschsprung disease

Malrotation with volvulus

Necrotizing enterocolitis

*Take a moment to consider the diagnosis in this infant.*

## **Actual Diagnosis**

### ***Hirschsprung Disease***

Although the contrast enema study did not reveal a transition zone, the dilated bowel seen in that study as well as the initial abdominal radiograph suggested a mid- or distal bowel obstruction, such as one seen with Hirschsprung disease.

Suction rectal biopsy was performed twice at the bedside, but the specimens were inadequate for diagnosis. Therefore, the patient underwent a near-full-thickness posterior rectal biopsy in the operating room. The specimen revealed no ganglion cells and neural hypertrophy, confirming the diagnosis of Hirschsprung disease or colonic aganglionosis.

The patient underwent laparoscopic-assisted endorectal pull-through procedure at 19 days after birth. Biopsies of the rectum and the sigmoid, descending, and transverse colons were obtained, and an appendectomy was performed. Ganglion cells were identified in the appendix and transverse and descending colons, but not in the rectum and sigmoid colon. The surgeon pulled through an area proximal to the biopsy site of the descending colon near the splenic flexure as a neoanus. This site also was biopsied and demonstrated ganglion cells.

## **The Experts**

### ***Approach to the Infant Who Has Abdominal Distension***

Proximal obstructions generally do not present with generalized distension unless perforation has occurred. When the obstruction is distal, as in malrotation with volvulus and meconium ileus, bilious vomiting may be seen. An important historic factor is the passage of meconium, which is delayed or absent in distal obstructions, such as in Hirschsprung disease or meconium plug syndromes. However, even in Hirschsprung disease, 50% of affected infants pass meconium by 24 hours of age.

Physical examination findings may include masses in meconium ileus/pseudocyst. Tenderness and erythema suggest perforation or peritonitis. Surgical consultation should be obtained while the patient is prescribed nothing by mouth (NPO) and an orogastric tube is placed to suction for decompression. Patients who have sepsis or other critical illness may present with signs of abdominal distension or obstruction and should be treated for possible infection and stabilized prior to determining the cause of obstruction. Fluid resuscitation should be provided. Plain films should be obtained to rule out perforation or necrotizing enterocolitis, but they often reveal only nonspecific findings of bowel distension. The next step in radiographic evaluation often is a contrast enema. If that shows normal results, an upper

gastrointestinal contrast series may be warranted. An upper gastrointestinal radiographic study may be the first evaluation if the clinical picture is highly suggestive of malrotation with volvulus.

### ***Hirschsprung Disease***

Hirschsprung disease is named after a Danish pediatrician who reported the cases of two boys who had congenital megacolon and died from severe constipation and distension in 1888. The disorder occurs in 1 in 5,000 live births and is characterized by aganglionosis in the myenteric (Auerbach) and submucosal (Meissner) plexuses of the distal colon. Males are affected more than females. In 80% of cases, only the rectum and sigmoid colon are involved. In the remaining 20% of cases, the aganglionic component extends to the proximal colon.

There is an increased risk of the disorder in siblings (2.4% to 9%) compared with the general population. Autosomal dominant, autosomal recessive, and polygenic forms have been described. It is seen in association with genetic syndromes such as Down syndrome and Waardenburg syndrome. Eight genes have been implicated in Hirschsprung disease. The receptor tyrosine kinase RET proto-oncogene is involved in 50% of nonsyndromic cases. Receptor tyrosine kinases are cell surface molecules that are involved in signal transduction for cell growth and differentiation. RET is expressed in the developing nervous system. One autosomal dominant form of Hirschsprung disease has been mapped to chromosome 10q11.1, with an associated mutation in RET. Work continues on elucidating the genetics of the disorder.

In select uncomplicated cases, surgical correction can be accomplished by laparoscopically assisted primary pull-through or transanal pull-through procedures. If the patient has signs of enterocolitis, is critically ill, or has significant proximal distension, a staged reconstruction is undertaken, with initial colostomy and subsequent anastomosis, when the patient is deemed ready.

### ***Diagnosing Hirschsprung Disease***

The presence of a rectosigmoid transition zone on barium enema examination is highly predictive of Hirschsprung disease. However, a negative enema examination does not necessarily rule out disease. The level of the transition zone on radiographic analysis does not always predict the pathologic transition zone, particularly in long-segment disease.

Anorectal manometry is another method of diagnosing Hirschsprung disease. False-positive and false-negative results are potential problems with this test. In one series of children, a definitive diagnosis was made in 95% of patients. However, this number was decreased to 81% for patients in the immediate neonatal period. Anorectal



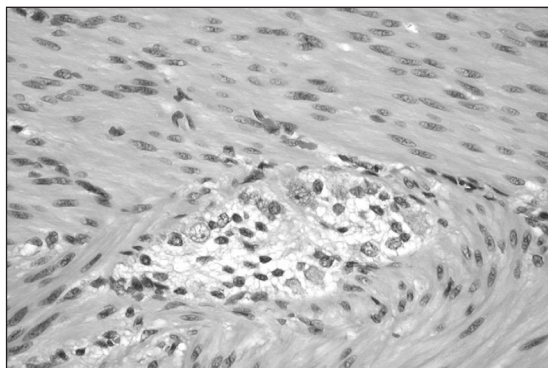
manometry may be useful in the context of predicting the absence of disease when the result is clearly negative, but for definitive diagnosis, supplemental testing often is required.

Rectal suction biopsy is diagnostic and should be performed when Hirschsprung disease is suspected. However, as seen in this case, a full-thickness biopsy is necessary to confirm the diagnosis when suction biopsy specimens are inadequate. Radiographic studies and manometry are least sensitive in the immediate newborn period. Thus, if Hirschsprung disease is suspected in the first few days after birth, biopsy often is the most useful evaluation. As in this case, the diagnosis may be somewhat delayed due to the necessity of waiting for results before proceeding to the next evaluation.

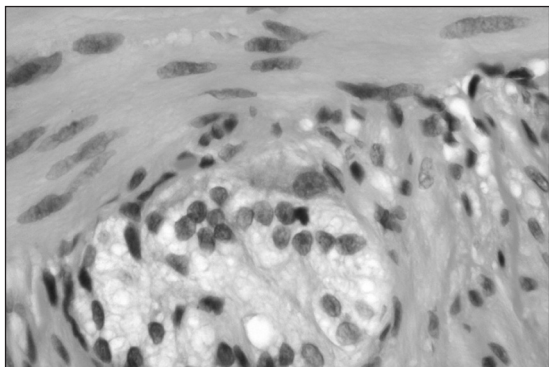
Acetylcholinesterase histochemistry also has been used by pathologists to diagnose Hirschsprung disease. Disease is suggested by the presence of many coarse, discrete cholinergic fibers in the muscularis mucosae and in the immediately subjacent submucosa.

## **Pathology**

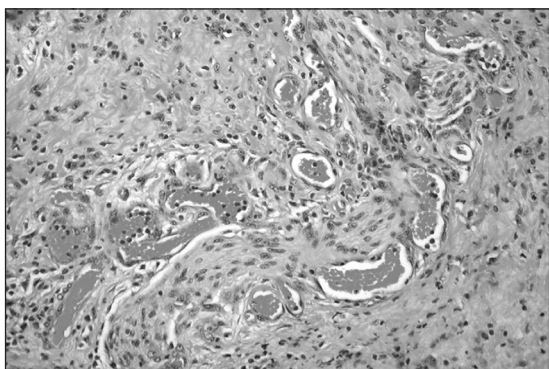
This 19-day-old infant was diagnosed with Hirschsprung disease by biopsy and subsequently underwent resection of the aganglionic segment of the bowel. The colon resection demonstrated neural hypertrophy and lack of ganglion cells distally. Ganglion cells were identified between the muscle layers of the muscularis propria in the proximal segment of the resected colon. In Hirschsprung disease, the narrowed distal bowel segment shows an absence of ganglion cells in both the submucosal plexus and the myenteric plexus. There usually is an associated hypertrophy of the muscularis mucosa layer and neural hypertrophy in the submucosa and in the muscularis propria, as seen in this case.



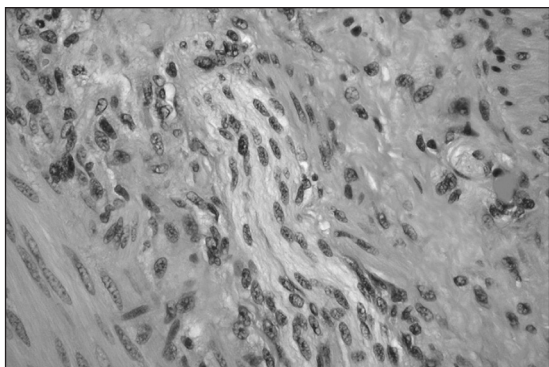
**Figure 19.4A.** Slide 1 of the proximal colon reveals ganglion cells (the cells with the prominent nucleoli and purplish cytoplasm).



**Figure 19.4B.** Slide 2 of the proximal colon also demonstrates one ganglion cell.



**Figure 19.4C.** In Slide 3 of the distal resected colon, there are no ganglion cells, and neural hypertrophy is demonstrated.



**Figure 19.4D.** Slide 4 of the distal colon also lacks ganglion cells and has neural hypertrophy.

Henry Chong Lee, MD, Kirsten Woolf, MD, Division of Neonatology and Department of Pathology, Stanford University, CA

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## **A Preterm Newborn Who Has Abdominal Ascites**

### **The Case**

A 36-weeks'-gestation preterm girl born by cesarean section due to abdominal ascites and nonreassuring fetal tracings.

### ***Prenatal History***

16-year-old G4P1021 Hispanic mother.

Blood group O+ (antigen screen-negative), hepatitis B surface antigen-negative, human immunodeficiency virus-negative, rubella immune, cytomegalovirus-negative, toxoplasmosis-negative, parvovirus-negative.

Mother refused amniocentesis.

Ultrasonography on the day of delivery showed polyhydramnios and abdominal ascites.

Fetal echocardiography revealed tricuspid regurgitation.

### ***Birth History***

Cesarean section due to nonreassuring fetal tracings, cephalic presentation, no meconium, no nuchal cord.

Infant appeared floppy after birth, with Apgar scores of 5 and 8 at 1 and 5 minutes, respectively.

Due to poor respiratory effort and increased abdominal girth with ascites, the infant was intubated emergently with a 3.5-French endotracheal tube, and bagged with 100% oxygen; after placement of an orogastric tube, scanty clear secretions drained.

## ***Case Progression***

### ***Vital Signs***

Temperature: 97.8°F (36.6°C)

Heart rate: 166 beats/min

Respiratory rate: 46 breaths/min

Blood pressure: 54/27 mm Hg

No visible discomfort

### ***Physical Examination***

Birthweight: 2,775 g (50th percentile)

Length: 42 cm (<10th percentile)

Occipitofrontal circumference: 33 cm (70th percentile)

Head, eyes, ears, nose, and throat: Normocephalic, normal facies, nares patent, no cataracts, normal ears, palate intact with oral endotracheal tube in place, no goiter

Lungs: Coarse breath sounds, equal bilaterally, deep intercostal retractions present

Heart: Normal S1, S2; regular rhythm; 1/6 systolic ejection murmur, quiet precordium; equal peripheral pulses

Abdomen: Firm, grossly distended abdomen, liver palpated 4 cm below the right costal margin, palpable splenic tip, umbilical hernia, kidneys nonpalpable, 3 vessels in the umbilical cord

Genitalia: Normal female, labia majora and labia minora equally prominent

Extremities: Hips stable, no deformities

Anus: Patent

Spine: Aligned, no hair tufts or dimples

Neurologic evaluation: Sleeping but awakens easily, appropriate response to painful stimuli, head lag present, appropriate strength and tone, positive grasp, suck noted, moving all limbs

Integument: No rashes, lesions, petechiae, or jaundice

### ***Initial Hospital Management***

Due to increased abdominal girth and subsequent respiratory distress plus initial arterial blood gas findings of pH 7.23, PCO<sub>2</sub> 57 mm Hg, PO<sub>2</sub> 48 mm Hg, HCO<sub>3</sub> 24 mmol/L, base excess, and -4 mEq/L, the patient was placed on a ventilator with

synchronized intermittent mandatory ventilation mode: FiO<sub>2</sub> 0.9, positive inspiratory pressure of 21 cm H<sub>2</sub>O, positive end-expiratory pressure of 5 cm H<sub>2</sub>O, 40 breaths/min, and pressure support of 5 cm H<sub>2</sub>O.

Surgical consultation, chest and abdominal films, cardiac consultation, and abdominal and pelvic ultrasonography were ordered.

Blood specimens were sent for culture, complete blood count, comprehensive panel, and karyotype.

Ampicillin and gentamicin were administered.

The infant was kept nothing by mouth, a percutaneous line was placed, and subsequent parenteral nutrition was initiated.

Repleg tube was placed and put on low intermittent suction.

### ***Radiologic Findings***

Chest and abdominal film: Endotracheal tube in good position, lungs inflated to 7.5 ribs, no infiltrate, no pleural effusions, no air leak, high right diaphragm, normal cardiac silhouette, orogastric tube in stomach, normal bowel gas pattern with no air in rectum (Figure 20.1).

Stat echocardiography: Mildly dilated atria with tricuspid regurgitation; no structural heart defects.

Head ultrasonography: Normal.

Abdominal ultrasonography: Enlarged liver; 2×1×1 cm fluid-filled, intrahepatic cyst; normal common bile duct; gallbladder with sludge; no intrahepatic ducts; ascites (Figure 20.2); no splenic enlargement; normal kidneys, bladder, and ovaries.



**Figure 20.1.** Chest radiograph.



**Figure 20.2.** Ultrasonography showing intrahepatic cyst.

***Pertinent Laboratory Findings***

Hemoglobin of 11.9 g/dL (119 g/L), hematocrit of 35% (0.35).

Total protein of 4.6 g/dL (46 g/L), albumin of 2.0 g/dL (20 g/L).

White blood cell count, differential count, electrolytes, fractionated bilirubin, liver functions, cultures, and karyotype normal.

***Differential Diagnosis******Neonatal Ascites***

Arteriovenous malformation

Biliary atresia

Choledochal cyst

Chylous ascites

Congenital lymphatic obstruction

Congenital infection (cytomegalovirus, syphilis, toxoplasmosis)

Congenital nephrosis

Fetal appendicitis with rupture

Galactosemia

Hepatitis

Imperforate anus

Intestinal atresia

Intrahepatic tumor or cyst

Major congenital cardiac disease

Meconium peritonitis with perforation

Mucopolysaccharidosis type VII

Perforation of Meckel diverticulum

Posterior urethral valves

Severe anemia due to thalassemia

Spontaneous common bile duct perforation

Supraventricular tachycardia

*Take a moment to consider the diagnosis in this infant.*

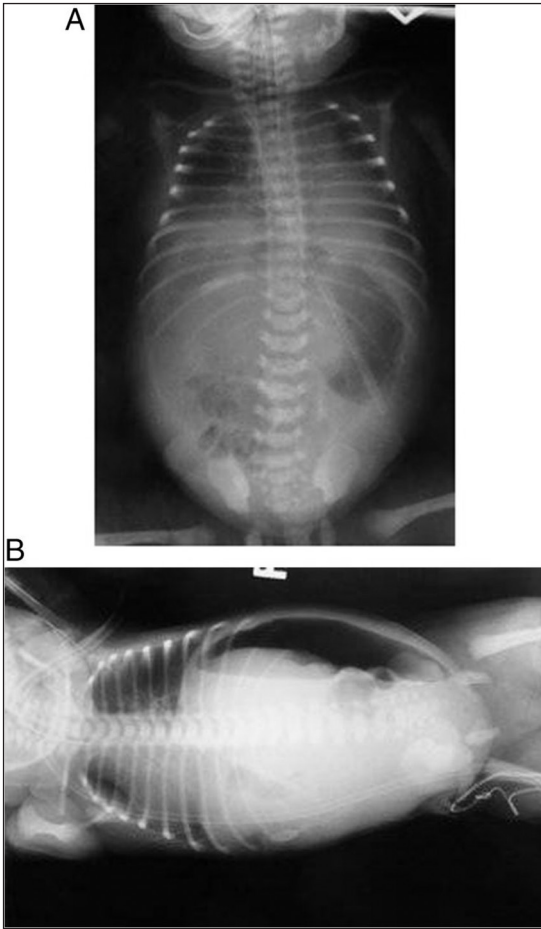


## **Actual Diagnosis**

### ***Hepatic Flexure Colonic Atresia With Perforation***

Initially, the abdominal ascites was believed to be due to either a vesicourethral outlet obstruction (the most common cause of ascites) or intestinal atresia (because of the maternal polyhydramnios). The nonpalpable kidneys on physical examination, brisk urine output, and normal findings on renal ultrasonography argued against vesicourethral outlet obstruction. The plan was to evaluate blood for beta-glucuronidase deficiency if radiography and ultrasonography findings were normal. Although mucopolysaccharidosis is rare, this diagnosis should be entertained in the presence of hepatomegaly, tricuspid regurgitation, anemia, and a negative TORCH screen, as reported in this case.

The initial flat plate abdominal film (Figure 20.1) appeared normal, except for the presence of ascites. Abdominal ultrasonography shortly thereafter showed an intra-hepatic cyst (Figure 20.2). The radiologist believed that this could not be a choledochal cyst because the biliary tree was visualized easily and appeared normal. A cross-table abdominal film was obtained to ensure that the cyst was truly loculated and not the result of transmitted free air within the abdominal cavity. The cross-table film showed a large amount of free air within the abdomen (Figure 20.3). The baby was taken to surgery in stable condition for an exploratory laparotomy, which revealed a hepatic flexure colonic atresia with perforation. The operating surgeon suggested that the perforation occurred in utero, sealed over, then reperforated after birth. Due to the inadequacy of ultrasonography in detecting free air, the pathology within the bowel that created the free air masqueraded as a hepatic cyst. Right colon resection and a colostomy were performed.



**Figure 20.3.** Abdominal flat plate and decubitus chest radiograph showing free air.

## The Experts

Intestinal atresia is a relatively common cause of bowel obstruction in the newborn, occurring most commonly in the jejunum and ileum. The colon is the least likely site of atresia, accounting for only 7% to 10% of cases. Congenital intestinal atresias are due to late intrauterine mesenteric vascular accidents. Rarely, jejunoileal atresia may be caused by failure of recanalization of the intestinal lumen occluded by epithelial cells. There are four possible types of colonic atresia: type I or membranous atresia; type II, in which the atresia consists of a thin fibrous band; type III or complete atresia that has no connecting band; and type IV or multiple atresia. The colon proximal to the atretic site is greatly dilated and contains air and meconium. Contrast studies are helpful in delineating the location of the atresia. A barium enema can show a shortened colon with a microcolon caliber. In 20% of cases, colonic atresia

is accompanied by other atresias. The common presentation for colonic atresia is abdominal distention, failure to tolerate feedings, and bilious emesis during the first 2 postnatal days, with failure to pass meconium. Although maternal polyhydramnios commonly is noted in proximal intestinal obstructions, it is uncommon in distal small bowel or colonic obstructions. Abdominal films show dilated loops of bowel, with pneumoperitoneum seen in 10% of cases. The site of obstruction is further distal, there are a greater number of dilated loops of bowel, and air fluid levels are present. It is important to obtain two views of the abdomen when confronted with suspected abdominal pathology. As demonstrated by this case, ultrasonography is not useful in determining the presence or absence of free air.

Management of colonic atresia includes initial placement of a Replogle tube for decompression of the bowel as well as fluid and electrolyte management to correct any metabolic abnormalities. Ampicillin and gentamicin should be started in preparation for surgery. Typically, resection is accomplished, with placement of an ostomy bag until the child has time to grow. A second surgery to reanastomose the bowel can be performed at a later date at the surgeon's discretion.

The prognosis for colonic atresia is very good; most patients recover without complications.

Mary Joan Marron-Corwin, MD, and Mary Kathleen Thomas, MD, St. Vincent's Catholic Medical Center, New York, NY

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## **A Preterm Girl Who Has a Distended Abdomen and Absent Bowel Sounds**

### **The Case**

#### ***Prenatal History***

28-year-old gravida 3 para 1 mother. History of fetal demise of unknown cause at 39 weeks' gestation in previous pregnancy.

Blood type O+, rapid plasma reagin nonreactive, rubella immune, hepatitis B surface antigen-positive, and antibody screen-negative.

Fetal ascites noted on prenatal ultrasonography.

Admitted with preterm labor and premature rupture of membranes at 30 4/7 weeks gestational age.

#### ***Birth History and Presentation***

The infant was delivered by repeat cesarean section. Amniotic fluid was meconium-stained. After delivery, the infant was intubated, and meconium was suctioned from the trachea. Apgar scores were 5 and 8 at 1 and 5 minutes respectively. She was transported to the neonatal intensive care unit while intubated.

#### ***Case Progression***

The patient was edematous at birth. Surfactant was administered through the endotracheal tube. The patient's abdomen was distended, and an abdominal radiograph was obtained, with findings similar to the abdominal radiographs in Figures 21.1 and 21.2, showing peritoneal calcification, fluid and distension. An orogastric tube was placed for suctioning. Paracentesis was performed, with drainage of brown fluid. A surgical drain was left in place in the left lower quadrant. Subsequently, the patient was transferred to a referral center.

***Vital Signs***

Heart rate, 166 beats/min

Respiratory rate, 51 breaths/min

Blood pressure, 73/47 mm Hg

Oxygen saturation 97% on mechanical ventilation, 25% FiO<sub>2</sub>

Temperature, 99.5°F

***Physical Examination***

Weight, 2,530 g; length, 45 cm; head circumference, 33 cm

Overall appearance: Active and pink, intubated, generalized edema

Skin: No icterus or birthmarks

Lungs: Coarse breath sounds bilaterally

Cardiac Examination: Normal heart rhythm; no murmurs

Abdominal Examination: Distended abdomen; unable to detect organomegaly; abdominal drain in left lower quadrant draining brown fluid; absent bowel sounds

Genitourinary Examination: Normal female external genitalia; anus patent

Skeletal Examination: Normal spine; stable hips; no sacral defects; normal extremities

Neurologic Examination: Appropriate strength and tone

***Laboratory Evaluation***

White blood cell count,  $15.3 \times 10^3/\text{mcL}$  ( $15.3 \times 10^9/\text{L}$ )

Hematocrit, 32% (0.32)

Platelet count,  $236 \times 10^3/\text{mcL}$  ( $236 \times 10^9/\text{L}$ )

***Differential Diagnosis***

Intestinal duplication

Imperforate anus

Meconium peritonitis

Mesenteric cyst

Neuroblastoma

Teratoma

*Take a moment to consider the diagnosis in this infant.*

## **Actual Diagnosis**

### ***Meconium Peritonitis (With Pseudocyst Formation)***

The radiograph revealed fine areas of calcification in both the right and left upper quadrants of the abdomen, findings that are consistent with meconium peritonitis.

The infant underwent exploratory laparotomy, which revealed a large meconium pseudocyst filling most of the abdomen. The cyst was opened and drained, and the wall of the cyst was excised. The small bowel and colon appeared normal in length and rotation; there was no evidence of atresia. A perforation in the antimesenteric border of the distal ileum 3 cm proximal to the ileocecal valve was found and repaired.

## **The Experts**

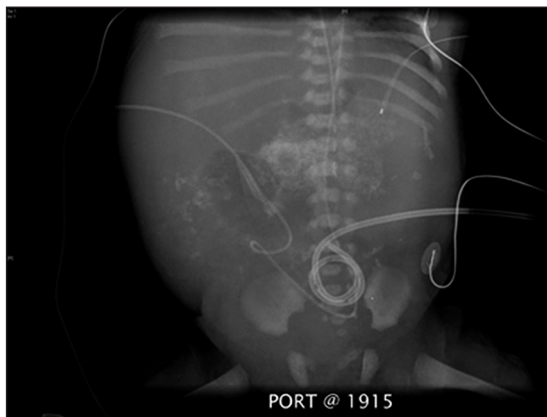
Meconium peritonitis is a sterile chemical peritonitis resulting from prenatal intestinal perforation. It occurs in 1 per 30,000 live births.<sup>1</sup> Perforation generally is due to congenital intestinal obstruction, such as meconium ileus, intestinal atresia, or volvulus. Intrauterine infection by cytomegalovirus, rubella, and parvovirus B19 also has been implicated.<sup>2,3</sup> Atresias may result from vascular accident. Because meconium ileus is due to cystic fibrosis in up to 15% to 40% of cases, depending on geographic region, testing for cystic fibrosis should be performed in patients who have meconium peritonitis. Many cases of meconium peritonitis have no clear cause.<sup>4,5</sup>

Meconium peritonitis can be diagnosed on prenatal ultrasonography. Polyhydramnios and fetal ascites are common, and fetal hydrops also has been described. In one series, calcification was seen in less than 50% of cases.<sup>4</sup> The patients whose only prenatal findings were fetal ascites had benign outcomes, with no need for surgical intervention. When no other findings are present, expectant management with serial ultrasonography may be adequate.<sup>2</sup> Compared with prenatal ultrasonography, postnatal radiographs or computed tomography scans are superior in detecting areas of fine calcification. When there is high suspicion, prenatal magnetic resonance imaging may assist in the diagnosis.<sup>4,6,7</sup>

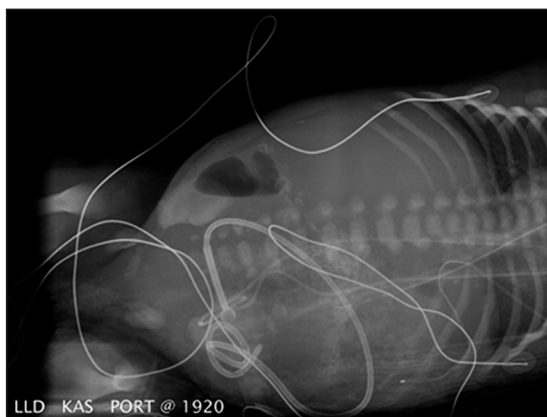
Leakage of meconium into the peritoneum leads to inflammation and ascites, which may result in the formation of a fibrous wall around the meconium. This pseudocyst then becomes calcified.<sup>2</sup> Aside from meconium peritonitis, calcified intra-abdominal masses may be due to intestinal duplication, hydrometrocolpos with imperforate anus, mesenteric cyst, neuroblastoma, Wilm's tumor, teratoma, hepatoblastoma, adrenal hemorrhage, adrenal cyst, giant Meckel diverticulum, and Hirschsprung disease.<sup>5,8</sup>

Although the diagnosis of meconium peritonitis and pseudocyst carried a poor prognosis in the past, advanced imaging techniques as well as progress in therapies, including surgical and neonatal care, have resulted in better outcomes.<sup>4,5</sup> Patients requiring surgery generally present with evidence of abdominal distention and acute abdomen. In such patients, timely intervention is essential; delayed surgery leads to a poorer prognosis.<sup>9,10</sup> However, in asymptomatic patients who have an incidental finding of calcifications, no intervention may be needed.<sup>8</sup>

*Henry Lee, MD, Stanford University Medical Center, Stanford, CA*



**Figure 21.1.** Abdominal film in the supine position demonstrating multiple areas of calcification consistent with meconium peritonitis; tubing from the surgical drain is also noted.



**Figure 21.2.** Abdominal film in the lateral recumbent position demonstrating calcifications and an air-fluid level within bowel loop or within a cyst.

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### COMMENTARY BY DR JOSEF NEU, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE

Going back to the older literature on a topic is often of interest. In a review of 12 cases of meconium peritonitis with and without calcifications,<sup>1</sup> the presence or absence of calcifications did not clearly relate to the subsequent diagnosis of cystic fibrosis, despite previous literature that stated that the presence of intraperitoneal calcification in meconium peritonitis excludes the diagnosis of cystic fibrosis.

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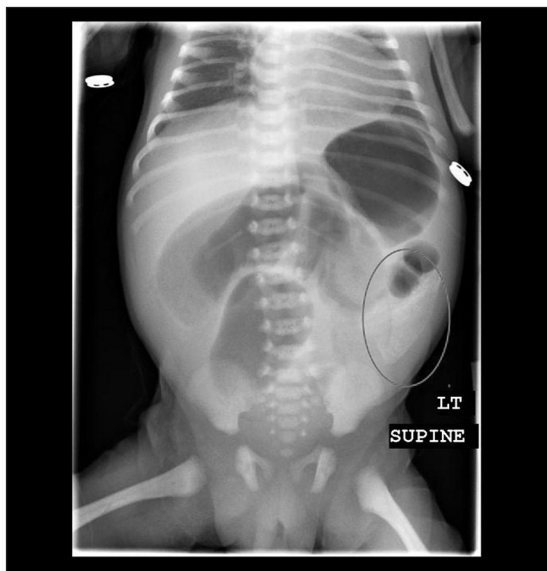
## Late Preterm Infant With an Abdominal Mass

### Presentation

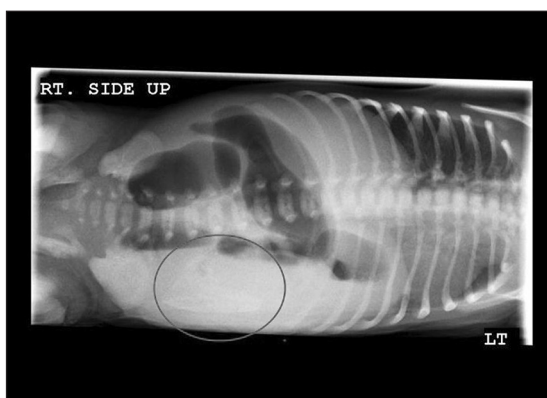
A late preterm white infant boy has a small bilious “spit-up” at 12 hours after birth. He was born at 36 3/7 weeks to a 23-year-old G2P0 mother. Maternal prenatal history is positive for 15 cigarettes per day during pregnancy; positive Chlamydia, for which she was treated; and positive group B Streptococcus. The mother received 2 doses of penicillin for her group B Streptococcus status more than 4 hours before delivery. He was delivered via vaginal delivery after spontaneous rupture of membranes lasting less than 18 hours. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively.

His measurements were appropriate for gestational age with a birthweight of 2,630 g and 37 weeks by Ballard examination. The boy has some dysmorphic features, including mild upward-slanting palpebral fissures, overriding sutures, and possible micrognathia. Examination is significant for a soft, nondistended abdomen with bowel sounds in four quadrants. A small, nontender, stool-like mass is palpated in his left lower quadrant. Rectum is patent. The mother is breastfeeding well, and the infant has adequate urine output. Stooling is delayed until 33 hours. He passes two 3-cm meconium plugs after rectal stimulation and one 3-cm meconium plug several hours later spontaneously. At 12 hours of age, he has an episode of bilious spit-up after which abdominal girth is monitored and ranged from 32.5 to 33.5 cm. At 46 hours after birth, he has an episode of large bilious emesis. Abdominal radiographs in the supine and left decubitus positions reveal no free air or pneumatosis, but reveal gaseous dilatation of the stomach and large bowel, large amounts of stool within the colon, and an unidentifiable triangular-shaped density in the left lower abdomen measuring approximately  $4 \times 2$  cm (Figures 22.1 and 22.2). A nasogastric tube is placed after 2 more episodes of bilious emesis. Metabolites are significant for an elevated chloride at 113 mmol/L and blood urea nitrate (BUN) of 35 mg/dL. C-reactive protein and serum bilirubin are within normal range, and a blood culture is negative. Weight is decreased to 2,400 g (9% loss). The rest of his examination

and vital signs remain unchanged. Intravenous fluids are attempted but access is not obtained. He is also found to have a patent foramen ovale, mitral and pulmonic regurgitation, and mild ectasia of the ascending aorta on echocardiogram. It is unclear if there is a genetic cause to his features and these findings, though all newborn screenings, coagulation studies, and cystic fibrosis (CF) microarray are negative. The infant is then given nothing by mouth and transferred to a tertiary care facility for exploratory laparotomy.



**Figure 22.1.** Abdominal film in the supine position demonstrating unidentified triangularly shaped density in the left lower quadrant, approximately  $4 \times 2$  cm, noted by a circle.



**Figure 22.2.** Abdominal film in the lateral recumbent position with the right side superior demonstrating the unidentified triangularly shaped density in the left lower quadrant approximately  $4 \times 2$  cm, noted by a circle.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

### *Case Progression*

After emergent exploratory laparotomy, the triangularly shaped defect is discovered in the left lower quadrant with many inflammatory adhesions. The midileal mass is adhered to the transverse colon; volvulus is noted. There is evidence of an in utero perforation secondary to meconium ileus; calcified meconium is adherent to the descending colon and ileum. The surgeon conjectures that the type I distal jejunoileal atresia was associated with complex meconium ileus.

### *The Condition*

The most common site of intestinal atresia is the midgut, with an incidence of 1 in 1,500 to 5,000 births. Of these, ileojejunal atresia is most commonly associated with extra-intestinal manifestations of malformations 43% of the time, with the most common being meconium ileus due to CF. Causes of meconium ileus not related to CF, as in this case, are less defined. Midgut intestinal atresia typically results from an acquired ischemic insult due to vascular disruption. In this case, maternal smoking exposure may be a factor in the vascular disruption associated with the atresia.

Most infants with intestinal obstruction are born at or near term. Symptoms of abdominal distension and multiple episodes of bilious emesis begin within 24 to 48 hours of age in atresia, but symptoms can be delayed for days to weeks if partially obstructed or stenosed. Infants may present with hyperbilirubinemia. Most fail to pass meconium. However, if the obstruction is more proximal, meconium passage may still occur. Abdominal tenderness may indicate peritonitis.

Intestinal atresia can be detected by prenatal ultrasound, especially if calcifications due to prenatal perforation are present. Ultrasound findings are often nonspecific in midgut atresia and include ascites, dilated bowel loops, and increased bowel echogenicity. Both supine anteroposterior and either an upright, lateral decubitus or cross-table lateral abdominal radiographs should be obtained to visualize dilated bowel loops and air-fluid levels. A complete blood count with differential, serum electrolytes, BUN, and creatinine levels should be taken. Mutation analysis for CF should be attained in midgut atresia, especially if meconium ileus or meconium plugs are present.

Women who smoke cigarettes or use vasoconstrictive drugs, including some allergy medications, during the first trimester are three times more likely to have infants with intestinal atresia; if the mother smoked greater than 20 cigarettes per day, that risk further increases by 4.2 times. Vascular ischemia is a main reason for midgut atresia, and maternal smoking or significant secondhand smoke exposure appears to

increase its risk. There is limited evidence related to causational effects of maternal smoking on the unborn child, and more research should be performed to determine those effects.

## ***Differential Diagnosis***

### ***Management***

The management of this case follows the standard of care for patients with complex meconium ileus with volvulus complicated by chemical peritonitis, inflammatory adhesions, and calcified meconium caused by in utero events. The pathology of the intestinal specimen revealed an obstructed portion of bowel with mural calcification, necrosis, and ischemic damage. This damage was consistent with in utero infarction or stenosis of normal or duplicated bowel. There was also jejunal focal atrophy of the outer circular muscle layer with venous congestion and calcified adhesions.

Genetic follow-up is scheduled, and at discharge all laboratory values were within the normal range or were followed to normalization in the outpatient setting. The true etiology behind his presentation is yet to be determined.

### ***Lessons for the Clinician***

Cystic fibrosis is the most common cause of meconium ileus. In most cases, intestinal atresia results from a vascular ischemic insult and has been associated with meconium ileus.

In cases of intestinal obstruction, the possibility of intestinal atresia should be considered in mothers who smoked during their pregnancies.

Infants typically present with failure to pass meconium and bilious emesis in the first 24 to 48 hours after delivery but can present later.

Abdominal plain films in the supine and lateral decubitus position can be helpful in diagnosis.

*Michelle L. Hobbs, BS, Fourth Year Medical Student, Ohio University Heritage College of Osteopathic Medicine; Beth McCloud, MD, Tara S. Williams, MD, Case Western Reserve University School of Medicine*

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### COMMENTARY BY DR JOSEF NEU, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE

One should always think of malrotation with volvulus in a newborn with bilious vomiting. This infant had an added complication of meconium ileus, which was likely related to the development of volvulus in this case. It is interesting to see these two entities together. The relationship between maternal smoking and atresias is fascinating.

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## Case 23

# Coagulopathy, Hepatomegaly, and Ascites in a Term Newborn

### Presentation

A full-term, small-for-gestational age boy is born via repeat cesarean delivery to a 30-year-old, now gravida 2, para 2 (0 preterm births, 0 losses before 20 weeks, and 1 living child) mother from an uncomplicated pregnancy. On routine newborn examination, the infant is found to have hepatomegaly (liver palpable 3 cm below the costal margin), ascites, and prominent bruising on the face and trunk. The remainder of the examination findings, including vital signs, are unremarkable. Laboratory work reveals a complete blood cell count notable for significant thrombocytopenia (platelet count of  $24 \times 10^3/\text{mcL}$  [ $24 \times 10^9/\text{L}$ ]) but is otherwise appropriate for a term infant. The aspartate transaminase and alanine transaminase levels are within the reference range. Blood glucose level is 40 mg/dL (2.2 mmol/L). Coagulopathy workup reveals a prothrombin time of 47 seconds, a partial thromboplastin time greater than 200 seconds, an international normalized ratio of 4.6, and a fibrinogen level of 50 mg/dL (1.5 mcmol/L). There is no family history of bleeding disorders. However, further questioning reveals the mother's only other pregnancy resulted in term neonatal demise of an unknown cause at 6 hours after birth. Autopsy was refused by the family at that time.

The patient is given cryoprecipitate and fresh plasma protein. Laboratory testing during the next few days reveals persistent coagulopathy. The results of all infectious workups are negative. Abdominal ultrasonography reveals a cirrhotic-appearing liver with features of portal hypertension and a patent ductus venosus. Other results include hyperbilirubinemia (total bilirubin, 15 mg/dL [256.6 mcmol/L]; direct bilirubin, 4 mg/dL [68.4 mcmol/L]), markedly elevated  $\alpha$ -fetoprotein level at 378,000 ng/mL (378,000 mcg/L), and an ammonia level of 143 mcg/dL (102 mcmol/L). Additional testing confirms the diagnosis.

*Take a moment to consider the diagnosis in this infant.*



## Discussion

Liver failure during the first days after birth has a broad differential diagnosis with numerous causes. However, acute liver failure in the absence of infection has a narrower differential diagnosis. One important cause in the newborn is gestational allo-immune liver disease (GALD), the major cause of neonatal hemochromatosis.

### *The Condition*

Although a rare condition, GALD is one of the most common causes of noninfectious liver failure in neonates and the most common cause of neonatal iron overload. It was once thought to be an inborn error of iron metabolism, with iron overload causing fetal liver injury. The iron deposition is now believed to be secondary to severe hepatic injury from an immune-mediated process. Specifically, GALD results from transplacental transfer of maternal immunoglobulin G (IgG) antibodies against a fetal hepatocyte antigen. The exact target is unknown. The antibody binding leads to complement activation with C5b-C9 membrane attack complex deposition on the cell surface, resulting in injury and cell death. Most fetuses will not survive the pregnancy, but the infants who do are generally born with profound liver failure. Gestational alloimmune liver disease may cause unexplained fetal demise during the late second and third trimesters.

### *Diagnosis*

Gestational alloimmune liver disease should be considered in all cases of neonates with signs of liver disease. Ultrasonography may detect prenatal signs, including ascites, fetal hepatomegaly, and fetal hydrops. Most neonates with GALD are found to be growth restricted and are prematurely born. Unexplained fetal demise during the late second and third trimesters should also lead the physician to suspect GALD as a possible cause. The classic presentation includes hypoglycemia and severe coagulopathy within the first few hours to days after birth. Common laboratory findings include an international normalized ratio greater than 4.5 (newborn reference range, 0.8–1.5), hyperammonemia (ammonia,  $>133$  mcg/dL [ $>95$  mcmol/L]), and hypoalbuminemia. The aspartate transaminase and alanine transaminase levels are normal or only minimally elevated because the liver damage generally occurs well before birth. Other findings include  $\alpha$ -fetoprotein levels greater than 100,000 ng/mL (100,000 mcg/L), with a mean of 300,000 ng/mL (300,000 mcg/L). Ferritin levels will be elevated at 800 to 10,000 ng/mL (1,798–22,470 pmol/L) (reference range, 40–775 ng/mL [90–1,741 pmol/L]), as will transferrin saturation levels (95%–100%). Lastly, severe thrombocytopenia (platelets,  $<50.0 \times 10^3/\text{mcL}$  [ $50.0 \times 10^9/\text{L}$ ]) will be found in 10% to 15% of GALD cases.

Definitive diagnosis is confirmed by iron deposition on extrahepatic tissue biopsy, usually of the oral mucosal salivary glands. If a liver biopsy is performed, immunohistochemical staining for the C5b-C9 complex will be present. Alternatively, T2-weighted magnetic resonance imaging (MRI) may be used to visualize hepatic and extrahepatic siderosis (most commonly seen in the pancreas, heart, and adrenal glands). In the appropriate clinical scenario, if the results of MRI or extrahepatic biopsy are negative, the other test should be ordered. On its own, each test is approximately 60% sensitive, but when the tests are performed together the sensitivity increases to 80%.

### **Management**

Postnatal management of neonatal hemochromatosis historically included chelation therapy and the use of antioxidants. This has since been replaced with double-volume exchange transfusion and intravenous immunoglobulin (IVIG) administration, which has decreased liver transplantation rates from 83% to 25% and has been associated with normal long-term liver function.

Unfortunately, the rate of lethal recurrence of GALD is estimated at 90% of subsequent pregnancies, making prenatal management crucial. If a pregnancy is subsequent to a prior known case of GALD, then treatment with IVIG, 1 g/kg, at 14 weeks' gestation is warranted. Intravenous immunoglobulin should again be administered at 16 weeks and weekly from the 18th week until the end of pregnancy. Research has found this regimen to be nearly 100% effective at preventing GALD.

### **Subsequent Course**

Additional testing revealed persistent thrombocytopenia, coagulopathy, hyperbilirubinemia (both direct and indirect), and a significantly elevated ferritin level (3,640 ng/mL [8179 pmol/L]), iron level (170 mcg/dL [30.4 mmol/L]), transferrin saturation level (100%), and iron-binding capacity (168 mcg/dL [30.1 mmol/L]). The patient had only minimal response to double-volume exchange transfusion followed by IVIG and was placed on a liver transplantation list. Unfortunately, he passed away shortly thereafter at age 1 week. Autopsy confirmed the diagnosis with iron deposition in mucosal and hepatic samples along with a cirrhotic-appearing liver.

## Lessons for the Clinician

Although rare, GALD is a common cause of noninfectious liver failure in neonates and the most common cause of neonatal iron overload.

Manifestations of GALD include intrauterine growth restriction, prematurity, hypoglycemia, marked coagulopathy, ascites, liver failure, hyperferritinemia, elevated  $\alpha$ -fetoprotein level, and patent ductus venosus.

The pathophysiology is alloimmune IgG attack to an unknown antigen on fetal hepatocytes, leading to C5b-C9 deposition and hepatocellular injury.

Previous pregnancy loss or neonatal death secondary to liver failure should prompt suspicion for GALD. When a previous sibling diagnosis has been made, prenatal IVIG should be given to the mother starting at 14 weeks' gestation.

Postnatal treatment of GALD includes IVIG and double-volume exchange transfusion. Appropriate and timely treatment has decreased the need for liver transplantation and has been associated with return of normal long-term liver function.

*Ridwaan Albeiruti, BS, Michigan State University-College of Human Medicine, Theodore E. Kelbel, MD, Helen DeVos Children's Hospital, Grand Rapids Medical Education Partners, Michigan State University-College of Human Medicine, Grand Rapids, MI*

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**COMMENTARY BY DR JOSEF NEU, UNIVERSITY OF FLORIDA  
COLLEGE OF MEDICINE**

Readers may want to refer to a review in *NeoReviews* that provides a more in-depth discussion of neonatal hemochromatosis and GALD, including a diagnostic algorithm and pictures of histologic sections with iron deposition in these diseases. Chu A, de Beritto TD, Kalpashri K, et al. Neonatal hemochromatosis: evaluation of the neonate with hepatic failure. *NeoReviews*. 2016;17(3):e154–e162

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# **An Extremely Low-Birthweight Infant Who Has Scrotal Discoloration**

## **The Case**

### ***Prenatal History***

39-year-old G3P0A2 Caucasian mother.

Infant born at 23 6/7 weeks gestational age.

The mother was admitted with premature onset of labor and was diagnosed with chorioamnionitis. She received a full course of antenatal betamethasone prior to delivery.

Blood group O+ (antigen screen-negative), hepatitis B surface antigen-negative, rubella immune, rapid plasma reagin nonreactive, group B Streptococcus screen unknown.

### ***Birth History***

Cesarean section (fetal distress). Apgar scores of 2 and 6 at 1 and 5 minutes, respectively.

Birthweight of 690 g.

### ***Hospital Course***

The infant had respiratory distress syndrome that required mechanical ventilation and 3 doses of exogenous surfactant; he was extubated to nasal continuous positive airway pressure on the eighth postnatal day. Additionally, he received 3 doses of prophylactic indomethacin during the first 72 hours after birth. His ductus arteriosus was closed upon completion of indomethacin treatment. He was treated with cefotaxime and ampicillin for the first 8 postnatal days for culture-negative presumed sepsis. Within the first 24 hours of birth, he received dopamine, an insulin infusion

to treat hyperkalemia, and nitric oxide for 36 hours due to refractory hypoxemia. His nutritional requirements were delivered with total parenteral nutrition; enteral feedings had not been started. He did not receive postnatal steroids.

Nine days after birth, he developed inguinal and scrotal discoloration (Figure 24.1). These findings were associated with hypotension (mean arterial pressure, 20 mm Hg), decreased urine output (0.13 mL/kg per hour), hypothermia (core body temperature of 96.4°F [35.8°C]), and 5 episodes of apnea and bradycardia that responded to bag and mask ventilation and tactile stimulation. On physical examination, the infant appeared pale. The abdomen was soft and scaphoid without masses. A right inguinal hernia reduced easily on examination, and testes were palpable in the inguinal pouch bilaterally. The scrotal and inguinal ecchymosis was remarkable.



**Figure 24.1.** Inguinal and scrotal discoloration in a newborn 9 days after birth.

Which studies would you obtain for further evaluation of this patient?

### ***Case Progression***

In response to findings on the physical examination, numerous laboratory studies were undertaken. Results included:

#### ***Hematology***

- White blood cell count,  $64 \times 10^3/\text{mcL}$  ( $64 \times 10^9/\text{L}$ )
- Hemoglobin, 12.3 g/dL (123 g/L)
- Hematocrit, 36.8% (0.368)
- Platelets,  $145 \times 10^3/\text{mcL}$  ( $145 \times 10^9/\text{L}$ )
- Fibrinogen 164 mg/dL (1.64 g/L)
- Prothrombin time, 13.2 sec

- Activated partial thromboplastin time, 233 sec
- International normalized ratio, 1.3
- C-reactive protein, 0.4 mg/dL

### ***Electrolytes***

- Sodium, 134 mEq/L (134 mmol/L)
- Potassium, 4.1 mEq/L (4.1 mmol/L)
- Ionized calcium, 5.3 mEq/L (5.3 mmol/L)

### ***Arterial Blood Gases***

- pH, 7.3
- PCO<sub>2</sub>, 58 torr
- PO<sub>2</sub>, 68 torr
- HCO<sub>3</sub>, 28 mEq/L

### ***Differential Diagnosis***

#### ***Scrotal Ecchymosis in a Preterm Newborn***

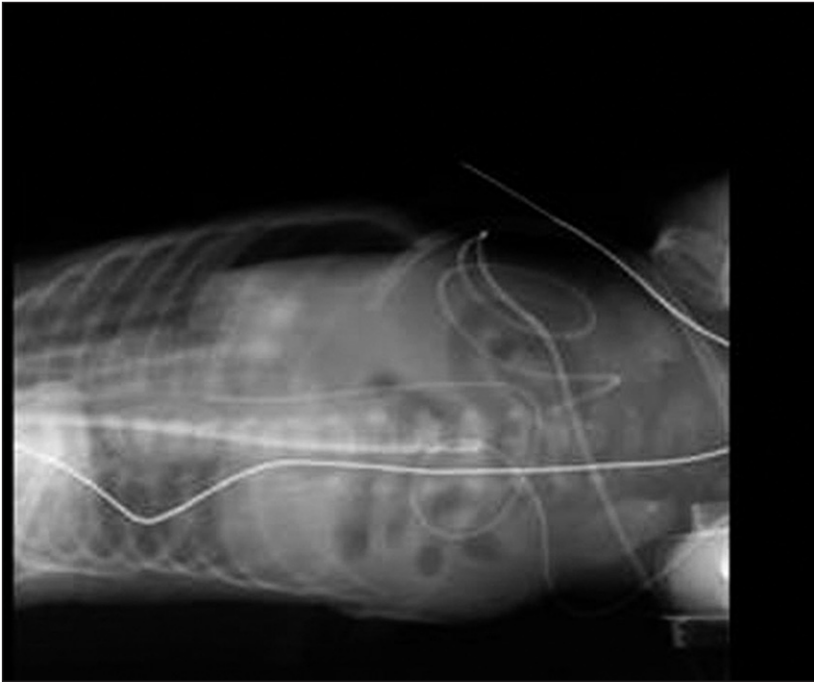
Incarcerated inguinal hernia

Bladder and urethral trauma

Hemoperitoneum and bleeding disorders, including thrombocytopenia (with or without disseminated intravascular coagulation), vitamin K deficiency, and hereditary factor deficiencies (hemophilia A/B).



## *Radiologic Evaluation*



**Figure 24.2.** A lateral decubitus abdominal radiograph reveals the diagnosis.

*Take a moment to consider the diagnosis in this infant.*

## **Actual Diagnosis**

### ***Spontaneous Bowel Perforation***

Supine and lateral decubitus abdominal radiographs revealed free air within the peritoneal cavity (Figure 24.2).

The patient's history, clinical findings, and laboratory study results were consistent with sepsis, most likely intra-abdominal in origin. The free air found in the abdominal radiographs was suggestive of perforation in the gastrointestinal tract, despite the lack of abdominal distention and peritoneal signs.

An emergency surgery consultation was requested, the patient was reintubated, and mechanical ventilation was restarted. Antibiotic coverage with metronidazole, cef-tazidime, and vancomycin was started. Surgery revealed a hemoperitoneum and a bowel perforation in the terminal ileum. Four centimeters of small intestine were resected, and an ostomy was created.

The presence of pneumoperitoneum in this case narrowed the differential diagnosis. Pneumoperitoneum can be due to perforation in the gastrointestinal tract, or its source can be the respiratory tract if signs of air leak are present. When pneumo-mediastinum, pulmonary interstitial emphysema, or pneumothorax is present, the peritoneal air collection is more likely to be of respiratory tract origin. In this case, those possibilities were excluded with a chest radiograph, which suggested the possibility of spontaneous bowel perforation.

## **The Experts**

### ***Pathophysiology***

The pathophysiology of spontaneous bowel perforation remains unknown. The distinction between necrotizing enterocolitis (NEC) and isolated intestinal perforation remains somewhat ambiguous. Currently there is no single unifying theory for the pathogenesis of these disorders. Four key risk factors have been identified for intestinal injury and NEC in neonates: prematurity, formula feeding, intestinal ischemia, and bacterial colonization. These factors promote the activation of epithelial cell apoptosis and bacterial translocation in the gut with the subsequent development of an inflammatory cascade within the intestinal wall that leads to bowel pneumatosis and perforation. Growing evidence supports the interactions between indomethacin and postnatal steroids as potentially contributing to isolated spontaneous bowel perforation.

## ***Clinical Features***

The incidence of NEC in infants weighing less than 1.5 kg ranges from 8% to 12%. Data from the National Center for Health Statistics and individual institutions suggest an incidence of 1,200 to 9,600 cases per year in the United States that result in more than 2,600 deaths annually.

Necrotizing enterocolitis usually occurs within the first postnatal week or within the first week after initiating enteral feeding. Its clinical presentation may vary from non-specific findings such as abdominal distention (the most frequent early sign in 70% to 98% of patients), ileus, feeding intolerance with emesis, and increased volume of gastric residuals or bilious aspirate from the nasogastric tube to frank signs of shock, blood per rectum, and peritonitis. Early systemic signs among patients who have NEC are typically nonspecific; they are similar to those seen with other causes of deterioration and sepsis, including labile temperature, apnea, and bradycardia.

## ***Treatment***

The treatment of NEC is medical during the early stages of the disease and medical/surgical if there is evidence of intestinal perforation or a deteriorating clinical condition. Medical management involves primarily supportive measures, including potential mechanical ventilation and circulatory support. If mechanical ventilatory support is necessary, tracheal intubation is preferred to prevent aerophagia and subsequent greater bowel distention; circulatory support begins with adequate fluid resuscitation and correction of acid-base imbalance. If there is evidence of coagulopathy, administration of platelets, fresh-frozen plasma, or cryoprecipitate may be indicated. After obtaining blood cultures, broad-spectrum antimicrobial therapy appropriate to cover bowel flora should be initiated, enteral feeding discontinued, and gastric decompression with a large-bore orogastric tube undertaken. Antimicrobials, as well as bowel rest, are continued for 7 to 14 days, depending on the severity of the episode.

If surgical management is indicated, the surgeon may remove the necrotic intestine, avoiding potentially viable intestine. A segment of intestine is used to create an enterostomy and mucous fistula. Primary resection and anastomosis of an isolated perforation is another surgical option in some cases. The use of primary peritoneal drainage for perforation is a possibility for some infants weighing less than 1.5 kg. This procedure involves making a right lower quadrant incision, irrigating the peritoneal cavity, and placing a small Penrose drain in the abdomen.

Scrotal and inguinal ecchymosis can be an early sign of hemoperitoneum in a pre-term baby who has a bowel perforation, even in the absence of other signs of intestinal ischemia and peritoneal inflammation. This can occur despite the lack of other clinical signs associated with intra-abdominal pathology, such as an increased amount of gastric residuals, enteral feeding intolerance, abdominal distention, and peritoneal signs.

Jose A. Ossa, Christopher E. Colby

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### COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER

The authors state that “NEC usually occurs within the first postnatal week or within the first week after initiating enteral feeding.” Based on our current knowledge, this is incorrect. More recent literature suggests that most cases of NEC peak at about 29 to 32 weeks’ postmenstrual age, so that an infant born at 26 weeks’ gestation will more likely develop the disease 5 weeks after birth and a 29-week gestational age infant will develop the disease 2 to 3 weeks after birth. Neu J, Pammi M. Pathogenesis of NEC: impact of an altered intestinal microbiome. *Semin Perinatol*. 2017;41(1):29–35.

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## **A Newborn Who Has Cystic Structures in the Lung**

### **The Case**

A term newborn female infant presents with respiratory distress, decreased breath sounds, and cystic structures in the left lung field visible on initial chest radiography. She was born to a 32-year-old G3P2 woman with good prenatal care.

#### ***Prenatal Laboratory Results***

Blood type: A+

Antibody screen: negative

Hepatitis B antigen: negative

Rubella: immune

Rapid plasmin reagin: nonreactive

Group B Streptococcus status: negative

Serum  $\alpha$ -fetoprotein: negative

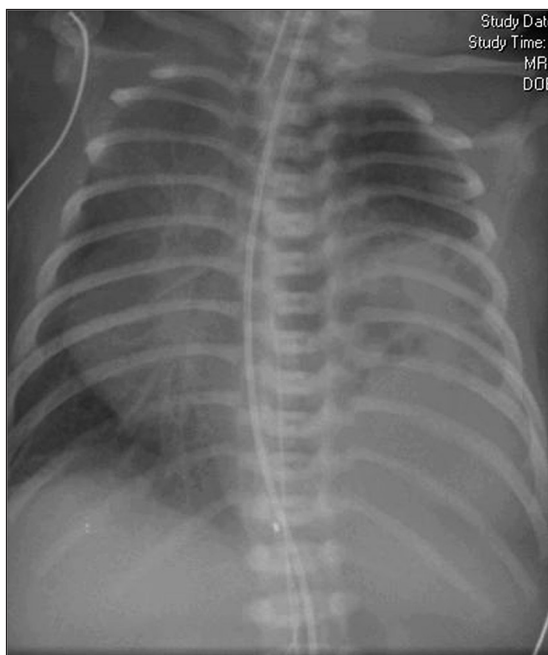
No amniocentesis was performed; normal results for 3 ultrasonographic studies performed during pregnancy.

Labor was induced at 37 2/7 weeks due to a history of macrosomia and severe shoulder dystocia in prior infants. Rupture of membranes occurred 2 hours prior to delivery.

The infant, whose birthweight was 3,860 g, was delivered by vaginal vertex delivery and initially was pale and floppy. She received bag-mask ventilation for 1 minute and continuous positive airway pressure (CPAP) for 5 minutes, resulting in improvement in tone and color. Apgar scores were 6 at 1 minute and 8 at 5 minutes.

The infant was admitted to the neonatal intensive care unit due to moderate grunting, flaring, and retracting. She had an oxygen saturation of 60% on room air and was started on nasal CPAP. Due to worsening tachypnea and respiratory distress, she was intubated at 30 minutes after birth.

Decreased breath sounds were notable at the left lung base. Chest radiography revealed cystic structures in the left lung field, with a rightward shift in the cardiac silhouette (Figure 25.1).



**Figure 25.1.** Radiograph revealed cystic structures in the left lung field, with a rightward shift in the cardiac silhouette.

## ***Case Progression***

### ***Laboratory Test Results***

#### ***Initial Arterial Blood Gas***

- pH, 7.31
- PCO<sub>2</sub>, 52 mm Hg
- PO<sub>2</sub>, 155 mm Hg
- Bicarbonate, 23
- Base deficit, 1.4
- Complete blood count, within normal limits
- C-reactive protein, negative
- Blood culture, negative

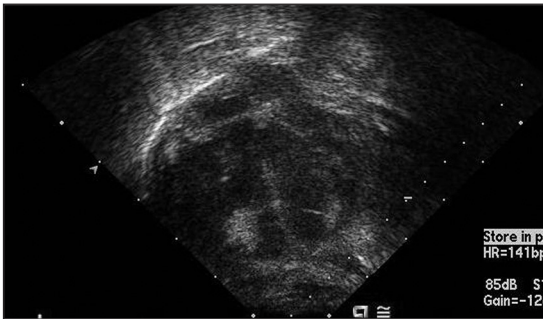
### *Management: Ventilator Settings*

- Peak inspiratory pressure: 20 cm H<sub>2</sub>O
- Positive end-expiratory pressure: 5 cm H<sub>2</sub>O
- Rate: 28 breaths per minute on spontaneous intermittent mandatory ventilation with an FiO<sub>2</sub> of 35% (0.35)

The infant remained stable on these settings, with oxygen saturations of 100%. A surgical procedure was performed on postnatal day 5 to correct her underlying problem.

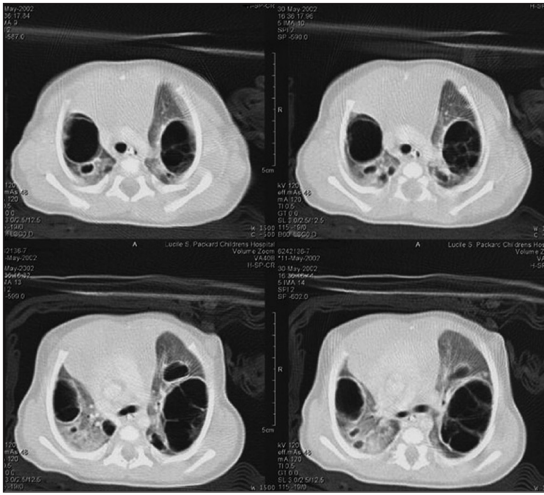
### *Further Studies*

- Electrocardiography showed normal sinus rhythm.
- Echocardiography showed multiple echogenic, intramural masses in the right and left ventricles (Figure 25.2). There was no evidence of inflow or outflow obstruction, and ventricular function was adequate.
- Chest radiography revealed cystic structures in the left lung field, with a rightward shift in the cardiac silhouette (Figure 25.1).
- Abdominal ultrasonography showed a possible cystic lesion in the liver, prompting an abdominal computed tomography (CT) (Figure 25.3).
- Abdominal CT showed a horseshoe kidney, but no liver or renal cysts.
- Voiding cystourethrography performed prior to discharge showed no evidence of reflux.
- Ophthalmologic examination results were within normal limits.
- Genetic testing showed a karyotype of 46XX. A specific genetic screen was performed, and results are pending at this time.



**Figure 25.2.** Echocardiography showed multiple echogenic, intramural masses in the right and left ventricles. There was no evidence of inflow or outflow obstruction, and ventricular function was adequate.





**Figure 25.3.** Abdominal ultrasonography showed a possible cystic lesion in the liver, prompting an abdominal CT. Abdominal CT showed a horseshoe kidney, but no liver or renal cysts.

## ***Differential Diagnosis***

### ***Cystic Lung Mass***

Bronchogenic cyst

Bronchopulmonary sequestration

Congenital cystic adenomatoid malformation

Congenital diaphragmatic hernia

Congenital lobar emphysema

Pneumatocele

### ***Cardiac Masses by Echocardiography***

Atrial myxomas

Cardiac fibromas

Fungal balls

Rhabdomyomas

Teratomas

*Take a moment to consider the diagnosis in this infant.*

## Actual Diagnosis

### *Congenital Diaphragmatic Hernia With Cardiac Rhabdomyomas and Possible Tuberous Sclerosis Complex*

The congenital diaphragmatic hernia was repaired laparoscopically. Evaluation for tuberous sclerosis was completed, and no other organ involvement was detected. The infant was discharged home with genetics and cardiology follow-up.

## The Experts

With increased use of prenatal ultrasonography, congenital diaphragmatic hernia (CDH) is diagnosed more commonly before birth. Undiagnosed cases present in the delivery room or shortly after birth with respiratory distress. These cases may be of late onset, allowing for better lung development and potentially smaller defect size. Breath sounds are absent on the left side, with displacement of the heart to the right. The chest may be barrel shaped and the abdomen scaphoid, with bowel sounds heard in the chest. The diagnosis is made by chest radiography with a nasogastric tube placed in the stomach, showing air-filled bowel loops in the chest. Contrast medium can be instilled to help distinguish CDH from cystic adenomatoid malformations in which multiloculated cysts can be mistaken for bowel loops in the thoracic cavity. Bronchogenic cysts are generally single, unilocular, spherical, and asymptomatic unless tracheobronchial communication exists.

Congenital lobar emphysema is the overinflation of a pulmonary lobe, potentially due to intrinsic or extrinsic bronchial obstruction. It occurs primarily in an upper lobe, and chest radiographs show a hyperinflated lobe with indistinct lung markings and atelectasis of the ipsilateral lung. Pulmonary sequestration is a mass of non-functioning, ectopic lung tissue with its own blood supply and no tracheobronchial communication. The mass usually is seen in the left lower lobe and is asymptomatic unless large enough to impinge on the surrounding lung. However, pulmonary sequestration is associated with congenital malformations in up to 50% of cases, including associated CDH. Pneumatocoles typically are acquired after pneumonia or in association with pulmonary interstitial emphysema or bronchopulmonary dysplasia.

A review of 166 cases of CDH in 1994 documented that 39% had associated anomalies, with two-thirds of these being a cardiac abnormality. Smaller studies have documented a 24% to 43% incidence of cardiac malformations with CDH. Associated cardiac anomalies have included hypoplastic left heart syndrome, atrial septal defect, ventricular septal defect, tetralogy of Fallot, coarctation, and Ebstein anomaly. Many anomalies involved the outflow tract. Therefore, it is important to evaluate all patients who have CDH with echocardiography.

Among infants who are younger than 1 year of age, the most common cardiac tumor is a rhabdomyoma. The incidence is rare, with equal distribution between the genders. More than 90% of primary tumors are benign. A solitary tumor arising from the ventricular wall is likely to be a fibroma. Left atrial tumors usually are myxomas, especially when pedunculated. An intrapericardial tumor arising near the great arteries most likely is a teratoma. Fungal masses usually involve the valves and occur rarely in the setting of severe fungal sepsis.

Rhabdomyomas usually are multiple, ranging in size from several millimeters to centimeters. The most common location is in the ventricular septum. It is important to evaluate for any obstruction to blood flow. It is also necessary to check for the presence of arrhythmias, the most common being ventricular tachycardia, supraventricular tachycardia, and Wolff-Parkinson-White syndrome. Surgical treatment is indicated only if the tumors create hemodynamic instability, although complete removal of the tumors is not always possible. Spontaneous regression of rhabdomyomas is common, and routine echocardiographic monitoring of tumor size is recommended in asymptomatic patients. Because more than 50% of patients who have multiple rhabdomyomas also have tuberous sclerosis, evaluation for additional organ involvement is suggested.

Tuberous sclerosis is an autosomal dominant disorder linked to mutations in the tumor suppressor genes *TSC1* and *TSC2*; it occurs in 1 in 300,000 individuals. Hamartomatous growths can be seen in the heart, brain, kidney, retina, skin, and liver. Children with this disorder are predisposed to difficulties with seizures and mental retardation if brain involvement occurs, although the presentation even within the same family is variable, and sporadic mutations occur in 60% of cases. Genetic testing is available on a research basis, but it is only 70% to 80% sensitive. Tuberous sclerosis cannot always be diagnosed immediately in the neonate. Revised diagnostic criteria were developed in 1998. Recommended initial testing includes an ophthalmic examination, electrocardiography, renal ultrasonography, and cranial CT or magnetic resonance imaging. The skin also should be examined thoroughly; hypomelanotic macules are the most common finding in children younger than 2 years of age. Manifestations of tuberous sclerosis may develop in other organs later in life, thus necessitating close follow-up and routine renal ultrasonographic evaluation. Horseshoe kidney is not typically associated with tuberous sclerosis. There has been only one case report of tuberous sclerosis and diaphragmatic hernia in the literature, making it difficult to substantiate a link between the two disorders.

*Valerie Chock, MD and JoDee M. Anderson, MD*

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*Part 6*

# **Genetics**

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## Bilateral Pedal Edema in a Newborn

### Presentation

A 1-day-old girl presents with bilateral pedal edema at birth (Figure 26.1). She was born at 37 weeks' gestation to a 29-year-old now gravida 5, para 3 mother who received poor prenatal care. The mother's blood type is O Rh+, she is rubella immune, and the results of serologic testing are negative for hepatitis surface antigen, syphilis, and HIV. Pregnancy was complicated by pancreatitis, and the infant was born via repeat cesarean delivery complicated by late decelerations. Her Apgar scores were 7 and 9 at 1 and 5 minutes, respectively.



**Figure 26.1.** Pedal edema.

On presentation to the nursery, the infant appears in no apparent distress, is alert, and has a weight of 3,020 g (20th percentile), a length of 46 cm (25th percentile), a chest circumference of 34 cm (>90th percentile), and a head circumference of 33 cm (50th percentile). Examination of the head is significant for posteriorly rotated auricles and high-arched palate. There are no abnormal pulmonary or cardiovascular findings. Her abdomen is soft and round, with active bowel sounds and



no organomegaly. Musculoskeletal examination shows bilateral edema to the feet with normal capillary refill and positive femoral and pedal pulses. The infant also has bilateral hypoplastic toenails (Figure 26.2).



**Figure 26.2.** Congenital lymphedema with puffiness over the dorsum of the feet and toes; narrow, deep-set nails.

Laboratory results include the following: white blood cell count,  $7.2 \times 10^3/\text{mcL}$ ; hemoglobin, 16.9 g/dL; hematocrit, 48%; platelet count,  $177 \times 10^3/\text{mcL}$ ; blood type, B+; direct antiglobulin test, positive; unconjugated bilirubin, 6.1 mg/dL; and reticulocyte count, 5.2%. One additional test reveals the cause of the pedal edema.

Cardiac echocardiography was performed and revealed a secundum atrial septal defect with an otherwise normal intracardiac anatomy. In addition, a renal ultrasound was ordered, which did not display any abnormalities. The results of her first newborn screen were negative for hypothyroidism, and the results of her otoacoustic emissions test were normal.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

### *Final Diagnosis*

Standard karyotyping demonstrated a single X chromosome, confirming the diagnosis of Turner syndrome (TS).

The differential diagnosis for bilateral pedal edema in a newborn includes congenital lymphedema (Milroy disease), congestive heart failure, hydrops fetalis, and TS. Milroy disease is a rare condition that is inherited in an autosomal dominant pattern and usually presents with bilateral lower-extremity edema and, at times, is associated with prominent leg veins, deep creases over the toes, papillomatosis, and hydroceles in boys. Congestive heart failure is unlikely in our patient because she does not have edema in other body parts, has a normal respiratory rate, has normal results for the cardiac examination, and has a normal liver span. Hydrops fetalis should also be considered; however, this usually involves an accumulation of fluid in two or more body areas caused by severe Rh incompatibility, heart failure, liver abnormalities, chromosomal anomalies, or prolonged anemia.

Turner syndrome is characterized by partial or complete absence of one X chromosome in some or all cells. This condition affects as many as 1 in 2,000 female live births, and some reports have stated that up to 10% of spontaneous abortions have a 45,X karyotype.<sup>1</sup> Although short stature and ovarian dysgenesis are classic findings, patients with TS are at risk for having multiple organ systems affected. Primary care clinicians must be aware of the morbidities associated with TS and manage the patient's care with appropriate subspecialists.

The diagnosis of TS should be considered in a female fetus/neonate if she presents with cystic hygroma, hydrops fetalis, edema to the dorsum of hands or feet, left-sided cardiac anomalies (coarctation of the aorta or hypoplastic left heart), low posterior hairline, broad chest with widely spaced nipples, and deep-set nails with prominent auricles.<sup>2</sup> During childhood and adolescence, patients will present with many of the findings seen in the neonatal period in addition to short stature, cubitus valgus, pterygium coli, amenorrhea, lack of breast development by 13 years of age, short fourth metacarpal, and a history of chronic otitis media.<sup>1</sup>

Turner syndrome may be difficult to diagnose because the distinctive features may not be present in some patients. The majority of prenatally diagnosed patients are found incidentally when mothers with advanced maternal age undergo chorionic villous sampling or amniocentesis. A retrospective study of 425 patients showed a delay in diagnosis with a mean age of 12 years.<sup>3</sup> In the neonatal period, lymphedema was the significant finding on physical examination, whereas short stature was the main finding in childhood or adolescence.<sup>2</sup>

Females with TS usually are of normal intelligence and perform normally in school. However, up to 10% will have significant delays that will not allow them to achieve independence in adulthood.<sup>4</sup> Despite an average IQ of 90, individuals with TS are at risk for delays in visual-motor skills, speech, attention, and nonverbal problem solving.<sup>5</sup> Socially, they can have difficulty understanding body language and facial expressions. As girls become older, they may be prone to anxiety, depression, and poor self-esteem.

## **Treatment**

A cardiac echocardiogram is recommended for all patients who are diagnosed with TS. Up to 40% of these patients may have a congenital heart defect, with left-sided lesions predominating.<sup>1</sup> Bicuspid aortic valve and coarctation of the aorta are among the more common cardiac lesions. Patients should also be evaluated at least annually for hypertension, because hypertension can be an early manifestation of aortic root dilatation. Some cardiologists perform echocardiographs as often as every 3 years to evaluate the aortic arch.<sup>5</sup>

At diagnosis, girls should also undergo a renal ultrasound to evaluate for anomalies. Horseshoe kidneys, a double collecting system, absent kidneys, malrotation, and multicystic/dysplastic kidneys are abnormalities present in 25% to 40% of patients with TS.<sup>2</sup> Although these anomalies usually are of no consequence, at times, they have been shown to increase the likelihood of urinary tract infections, hydronephrosis, and systemic hypertension.<sup>1</sup> In addition, hypertension can be seen even without cardiac anomalies.

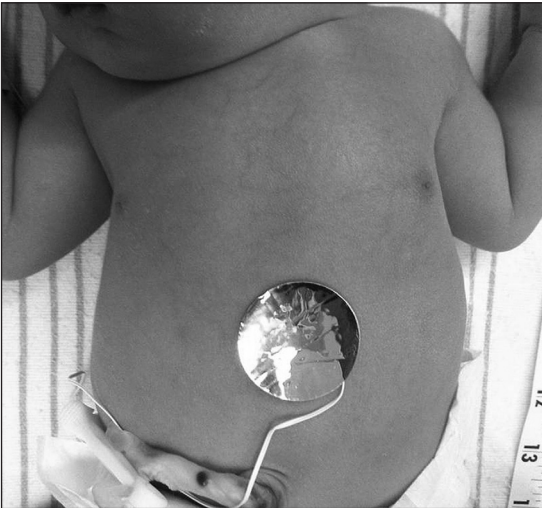
Ophthalmologic and otologic abnormalities are also common among patients with TS. Approximately 30% of patients have strabismus, and girls with TS can have amblyopia, ptosis, or color blindness.<sup>2,4</sup> More than half of women with TS have sensorineural hearing loss that is progressive.<sup>5</sup> Approximately 25% of adults will require hearing aids. They are also more prone to chronic otitis media putting them at risk for conductive hearing loss. Early placement of tympanostomy tubes is recommended for recurrent otitis media as girls with TS often have delays in speech.<sup>4</sup>

Autoimmune disorders, such as inflammatory bowel disease and celiac disease, are more frequent in individuals with TS.<sup>1</sup> Hypothyroidism increases with age; therefore, thyroid function tests should be measured at diagnosis and every 1 to 2 years.<sup>1,4</sup> Girls and women with TS have a predisposition to glucose intolerance; however, diabetes is uncommon. Proper diet and exercise should be encouraged during well-child visits.

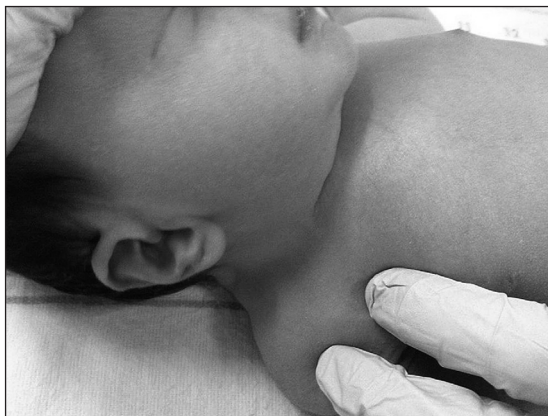
Orthopedic evaluation should include careful assessment for hip dislocation in newborns and examination of the back for scoliosis during adolescence.<sup>1,5</sup> Females with TS tend to be short and stocky with a wide internipple space (Figure 26.3). Endocrinologists usually begin growth hormone therapy when the patient has dropped below the fifth percentile of the normal female growth curve.<sup>1,4</sup> Discontinuation of growth therapy occurs when the bone age is 14 years and the velocity of growth has decreased by  $<2$  cm over the preceding year.

Webbed neck, low posterior hairline, and dorsal pedal edema are some of the more common characteristics in patients with TS (Figure 26.4).<sup>2</sup> These abnormalities are derived from a failure in the development of the lymphatic system. Lymphedema of the hands and feet are usually present at birth, but they resolve by 2 years of age.<sup>1</sup> There can be a recurrence of edema at any age; the edema can be controlled with support stockings or diuretics.<sup>4</sup>

More than 90% of girls with TS will have gonadal dysgenesis; however, as many as 5% of individuals will have menses. Thirty percent of females who have mosaic TS will spontaneously enter puberty, but, for the majority, estrogen therapy is necessary.<sup>4</sup> One must keep in mind that estrogen can cause premature closure of the epiphyses; consequently, it should be coordinated with the use of growth hormone. The initiation of estrogen treatment is important to allow feminization at the appropriate chronologic age.



**Figure 26.3.** Broad chest with widely spaced nipples.



**Figure 26.4.** Webbed posterior neck.

### **Lesson for the Clinician**

The most likely cause of bilateral dorsal pedal edema in a female newborn is TS.

*Alvaro Moreira, MD, Alejandro Diego, MD, Rafael Fonseca, MD, University of Texas Medical Branch at Galveston, Galveston, TX*

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*Part 7*

# **Hematology/Oncology**

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## Term Infant With Hepatosplenomegaly

### Presentation

A term female infant presents at 9 days of age with fever, feeding refusal, vomiting, diarrhea, and a large abdomen. She was born vaginally after an uneventful pregnancy and delivery to nonconsanguineous white parents, with a birthweight of 3.5 kg.

Mother is a 33-year-old gravida 2 para 1 sales assistant who is rubella immune and otherwise serology negative. A male sibling is well at age 21 months.

The family and travel histories are negative, and the early clinical course of the infant was unremarkable.

On examination, the infant is pale, jaundiced, febrile (temperature: 39°C), tachypneic (respiratory rate: 78 breaths/min), grunting, and tachycardic (heart rate: 189 beats/min), and she has hepatomegaly (7 cm below the right costal margin) and splenomegaly (5 cm below the left costal margin). No dysmorphic features are observed. She has bruises on different parts of the body. Her weight is 3.16 kg. The results of chest, heart, and neurologic examinations are normal, but she looks miserable and restless.

Blood investigations, including bacterial blood cultures and viral serology, are ordered, and initially she starts on phototherapy, IV fluids, IV antibiotics, and acyclovir.

Results: Hemoglobin (Hb), 3.8 g/dL; white blood cell (WBC) count,  $6.1 \times 10^9/\text{L}$ ; neutrophils,  $0.7 \times 10^9/\text{L}$ ; platelets,  $13 \times 10^9/\text{L}$ ; C-reactive protein (CRP), 44 g/L; serum bilirubin: total, 18.6 mg/dL; direct, 1.7 mg/dL; alanine aminotransferase, 870 U/L; alkaline phosphatase, 400 U/L; prothrombin time, 14.7 (normal: 9.6–11.8) seconds; activated partial thromboplastin time, 52 (normal: 28.0–40.0) seconds; international normalized ratio, 1.6 (normal: 1.2); negative Coombs test (direct and indirect). Sodium, potassium, calcium, phosphate, urea, and creatinine concentrations are all within normal limits. Blood gas analysis: pH, 7.34;  $\text{PCO}_2$ , 27 mm Hg (3.6 kPa),  $\text{PO}_2$ , 82.5 mm Hg (11 kPa);  $\text{HCO}_3$ , 18 mm Hg; base excess, -11; lactate,



6 mmol/L; blood glucose, 72 mg/dL (4 mmol/L). Chest radiograph shows no abnormality. Abdominal ultrasound examination confirms hepatosplenomegaly, and no other findings are reported.

A dose of vitamin K is given. Packed red blood cells, fresh frozen plasma, and platelets are transfused over the next 12 hours.

With no improvement, or clear identity of the etiology of the pancytopenia and hepatosplenomegaly during the next 2 days, further investigations are ordered.

Blood film shows a mixture of normal-sized mature and larger immature lymphocytes with prominent nucleoli and high nuclear:cytoplasmic ratio, and a few nucleated red blood cells in conjunction with pancytopenia.

Because of the possibility of acute lymphoblastic leukemia, bone marrow aspirate is performed, which shows mild erythroid dysplasia, poor maturation of the myeloid series, no infiltrates, no hemophagocytes, and no foamy macrophages or Gaucher cells.

Additional investigations are done, including ferritin, 390 (normal: 25–200) mcg/L; fibrinogen, 1.0 (normal: 1.70–4.0) g/L; and lactic dehydrogenase, 647 (normal: 100–300) IU/L.

Bacterial blood cultures and viral polymerase chain reaction for varicella zoster; herpes simplex; cytomegalovirus; Epstein-Barr; hepatitis A, B, and C viruses; and parvovirus all come back negative. Immunologic (immunoglobulins and lymphocyte subsets), HIV, and metabolic profiles all prove normal.

## Discussion

### *Clinical Progress*

She is maintained on phototherapy and IV antibiotics with no signs of improvement. Further clinical and laboratory deterioration is noted. Respiratory distress recurs with more pronounced signs, and blood gases become worse, necessitating endotracheal intubation and mechanical ventilation. Repeat blood results 5 days after admission show Hb, 5.3 g/dL; WBC count,  $5.4 \times 10^9/L$ ; neutrophils,  $0.5 \times 10^9/L$ ; platelets,  $42 \times 10^9/L$ ; bilirubin: total, 20.7 mg/dL; direct, 1.9 mg/dL (on triple phototherapy); CRP, 69 mg/L; ferritin, 2,675 mcg/L; fibrinogen, 0.4 g/L; and triglycerides, 89 mg/dL (1.01 mmol/L) (normal:  $<150 \text{ mg/dL} = 1.85 \text{ mmol/L}$ ).

The antibiotic combination is changed, and more blood products are transfused.

Negative blood and urine tandem mass chromatography rule out several inborn errors of metabolism.

Following the advice of the hematology and immunology teams, further investigations are requested, including soluble cluster of differentiation (CD) 25 receptor, 2,237 (normal: 200–1,000) U/mL; tumor necrosis factor- $\alpha$ , 106.8 (normal: <10) pg/mL; interferon- $\gamma$ , 726 (normal: 45) pg/mL; interleukin (IL)-2, 6.3 (normal: <4.5) pg/mL; IL-4, 5.9 (normal: <15) pg/mL; IL-8, 329 (normal: <50) pg/mL; IL-6, 102 (normal: <20) pg/mL; IL-10, 427 (normal: <15) pg/mL; IL-12, 65 (normal: <50) pg/mL; and IL-1 $\beta$ , 7 (normal: <5) pg/mL. Normal levels of perforin expression: 3.4% (normal: 0.3%–5.1%). Urinary  $\beta_2$ -microglobulin level: 2,270 (normal: <120) mcg/L.

*Take a moment to consider the diagnosis in this infant.*

The decision is made to treat for hemophagocytic lymphohistiocytosis (HLH), based on the following criteria: fever, hepatosplenomegaly, pancytopenia, high soluble CD25 (as part of a generalized hypercytokinemia), rising ferritin, and falling fibrinogen levels.

Criteria against this diagnosis were the absence of hemophagocytosis on the bone marrow aspirate, normal triglycerides, and normal perforin expression.

Treatment started using dexamethasone (10 mg/m<sup>2</sup>), etoposide (150 mg/m<sup>2</sup>), cyclosporine A (6 mg/kg), and intrathecal methotrexate, according to the HLH-2004 protocol, which is continued with clear clinical improvement. She is then discharged from the hospital on chemotherapy treatment for 8 weeks awaiting bone marrow transplantation.

## **Disease Process**

The term histiocytosis applies to a group of conditions that have in common the characteristics of proliferation and accumulation of antigen-presenting (dendritic) or antigen-processing (macrophage) cells.

Hemophagocytic lymphohistiocytosis is the most common macrophage-related disorder that represents a clinical syndrome encountered in association with various underlying diseases leading to similar characteristic clinical and laboratory presentations. It encompasses two different conditions, which may be difficult to distinguish: primary, denoting the presence of an underlying genetic disorder (familial HLH 1–5) or an immunodeficiency syndrome (Griscelli syndrome, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome type II, and X-linked lymphoproliferative syndrome type 1 and type 2), and secondary (acquired), denoting an association with either infection (mainly viral), malignancy, malignancy treatment-related immunosuppression, renal or liver transplantation (accompanying Epstein-Barr virus lymphoproliferative syndrome), or Kawasaki disease.<sup>1</sup> There is no specific test with the ability to quickly define these two categories, because the same gene mutations can be present in both situations, and, with few exceptions, the clinical presentation and outcome are the same for both.

An estimated incidence of 1 per 50,000 live-born neonates may be an underestimate reflecting diagnosis-related problems.<sup>2</sup>

The diagnosis is particularly difficult in the neonatal period. The rarity of the disease, the fact that many neonatologists are unaware of it, and the limited repertoire of clinical presentations in these patients, are all added to the common absence of the hallmark (hemophagocytosis) at an initial bone marrow examination, a procedure that is rarely performed in neonates.<sup>3</sup>

The natural course of the disease is classically characterized by intermittent or constant fever, pronounced hepatosplenomegaly, and cytopenia that may, in some patients, be accompanied by signs of early or evolving central nervous system involvement that may dominate the clinical course with progressive cerebromeningeal symptoms, including irritability, bulging fontanelle, tone abnormalities, and convulsions.

Most reports of HLH in neonates have been included in childhood HLH studies, and only very few reports tried to characterize neonatal HLH independently.

### ***Pathophysiology***

Although the basic deficiency remains to be clarified, hypercytokinemia is in the center of the pathophysiologic process. Low or absent natural killer (NK) cell and dysregulated T cell activity are thought to result in a highly stimulated, yet ineffective, multisystem inflammatory response to different microbial or tumorous antigens that cannot be fully eliminated, thus driving an uncontrolled and fatal antigen-specific T cell expansion.<sup>4</sup>

T cells continue to proliferate and produce a great quantity of cytokines, further activating and recruiting additional lymphocytes and inflammatory cells.

The end result is the accumulation of lymphohistiocytic infiltrates into organs, including the liver, spleen, lymph nodes, bone marrow, and central nervous system, with associated organ damage in addition to the systemic signs of hypercytokinemia. Activated macrophages may nonselectively engulf hematopoietic components, such as erythrocytes, leukocytes, platelets, their precursors, and cellular fragments, leading to the hallmark findings in the bone marrow or other organs of patients with HLH.<sup>5</sup>

## **Diagnosis**

The initial presentation of neonatal HLH may simulate a number of common conditions in this age group, such as respiratory distress syndrome, sepsis, meningitis, and multiple organ failure syndrome.

Cytopenias, usually thrombocytopenia, anemia, and, less frequently, neutropenia, are common at onset. High levels of circulating cytokines and organ infiltration are associated with various clinical and laboratory signs of HLH.<sup>6</sup> Depending on the degree of liver involvement, hepatic dysfunction may present as transaminitis, hyperbilirubinemia, hypoalbuminemia, and/or coagulopathies, in particular, hypofibrinogenemia, especially during active disease.<sup>1</sup>

Elevated ferritin, hyponatremia, and low proteins, as well as hypertriglyceridemia, are other common findings that are associated with the general inflammatory state.

Brain abnormalities may be seen on magnetic resonance or computed tomography imaging later in the course of prolonged disease as areas of past or ongoing inflammatory activity, or demyelinated areas, bleeding, atrophy, edema, or calcifications.<sup>3</sup>

Cerebrospinal fluid examination usually shows a moderate pleocytosis with mainly lymphocytes associated with elevated protein levels.<sup>4</sup>

## **Treatment**

Chemoimmunotherapy used in the treatment of HLH includes etoposide, dexamethasone, and cyclosporine A initially and, in selected patients, intrathecal therapy with methotrexate and corticosteroids. Subsequent hematopoietic stem cell transplantation is recommended for patients with underlying genetic mutations and severe and persistent, or reactivated, disease.<sup>7</sup>

Guidelines for diagnosing and treating HLH were introduced in 1994, and revised in 2004 by the Histiocyte Society, based on common clinical, laboratory, and histopathologic findings.<sup>8</sup>

In HLH-94, the first prospective international treatment study for HLH, diagnosis was based on 5 criteria (fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis). In HLH-2004, 3 additional criteria are introduced: low/absent NK cell activity, hyperferritinemia, and high soluble IL-2 receptor levels. All together, 5 of these 8 criteria must be fulfilled, unless family history or molecular diagnosis is consistent with HLH.

### ***Diagnostic Guidelines for HLH<sup>8</sup>***

The diagnosis of HLH can be established when 1 or 2 of the requirements below are fulfilled:

1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below):
  - a. Fever
  - b. Splenomegaly
  - c. Cytopenias (affecting  $\geq 2$  of 3 lineages in the peripheral blood)
    - i. Hb  $< 100$  g/L
    - ii. Platelets  $< 100 \times 10^9$ /L
    - iii. Neutrophils  $< 1 \times 10^9$ /L
  - d. Hypertriglyceridemia and/or hypofibrinogenemia
    - i. Fasting triglycerides  $\geq 3$  mmol/L (265 mg/dL)
    - ii. Fibrinogen  $\leq 1$  g/L
  - e. Hemophagocytosis in the bone marrow, spleen, or lymph nodes
  - f. Low or absent NK cell activity
  - g. Ferritin  $\geq 500$  mcg/L
  - h. Soluble CD25 (IL-2 receptor)  $\geq 2,400$  U/mL

Aside from some case reports, the only systematic study on neonatal HLH was a national Japanese survey conducted between 1997 and 2007.<sup>3</sup> Hemophagocytic lymphohistiocytosis was diagnosed in 20 (10 male, 10 female, 8 preterm, and 12 term) infants. The median age at diagnosis was 6.5 days, and HLH was diagnosed in 6 patients at birth. Of the 20 patients, 8 (40%) survived; 2 of 7 with familial or severe combined immunodeficiency HLH and 2 of 6 with herpes simplex virus HLH survived, respectively. The difference between survivors and nonsurvivors was not statistically significant in terms of laboratory findings, including lactate dehydrogenase, ferritin, soluble IL-2 receptor, and fibrinogen. The numbers are not big enough to draw conclusions, but may highlight potential differences between pediatric and neonatal HLH and warrant focusing on the latter as an independent entity.

## Lessons for the Clinician

Hemophagocytic lymphohistiocytosis is a rapidly fatal disease that may be very difficult to diagnose.

Hemophagocytic lymphohistiocytosis needs to be considered in any neonate with unexplained fever, hepatosplenomegaly, liver cell failure, and/or several other conditions.

Hemophagocytic lymphohistiocytosis can be particularly difficult to differentiate from sepsis, especially during disease reactivation, and both conditions may coexist.

Patients with HLH can deteriorate extremely rapidly with a “septic”-looking clinical picture (due to cytokine storm).

Adel Abdelhamid, MB BCH, MSc, Neonatal Unit, St Michael Hospital, Bristol University, Bristol, UK

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**COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER**

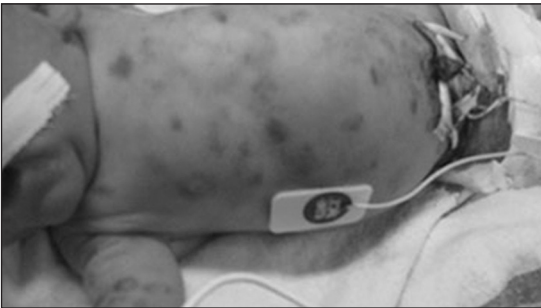
The 2004 diagnostic guidelines developed by the Histiocyte Society have not been revised. However, it is now recognized that a ferritin level greater than 10,000 ng/mL (22,470 pmol/L) has a high sensitivity and specificity for HLH (90% and 96%, respectively) and the decline in ferritin levels might be prognostic.<sup>1</sup> Recent data also suggest that primary and acquired HLH might represent the same disease process that exhibits a different clinical presentation based on risk (Figure 1).<sup>2</sup> A recent clinical trial to assess the combination of antithymocyte globulin, dexamethasone, and etoposide for the treatment of HLH has been completed, and results are pending (ClinicalTrials.gov, NCT01104025).

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## Blueberry Muffin Rash and Respiratory Distress in a Late-Preterm Infant

### The Case

A late-preterm infant presented with blueberry muffin rash and respiratory distress present at birth (Figure 28.1).



**Figure 28.1.** Blueberry muffin rash in a late-preterm infant.

### *Prenatal History*

- 28-year-old G1 mother with negative serologies, including rubella immune and rapid plasma reagin nonreactive
- Pregnancy complicated by preterm labor at 34 weeks, which resolved
- Mother presented at 36 weeks in labor with spontaneous rupture of membranes (clear fluid)
- Infant delivered by cesarean delivery because of fetal decelerations

### *Birth History and Presentation*

- Apgar scores 5, 5 at 1 minute and 5 minutes, respectively
- Intubated for respiratory distress shortly after birth
- Birthweight: 2,470 g (10%–50%)
- Length: 43 cm (3%–10%)
- Occipitofrontal circumference: 32.5 cm (50%)



## Case Progression

### Vital Signs

- Temperature: 37.4°C
- Heart rate: 140 beats per minute
- Respiratory rate: 57 breaths per minute
- Blood pressure: 66/36 mm Hg
- Oxygen saturation: 96%

### Physical Examination

- Intubated, mechanically ventilated
- No dysmorphic features
- Anterior fontanelle open, mildly to moderately full
- Bilateral coarse breath sounds
- Abdomen is full, with marked hepatomegaly, palpable spleen
- Diffuse, nonblanching, bluish-red macules, patches, and nodules generally smaller than 1.5 cm covering the scalp, face, chest, abdomen, back, extremities, and palmar and planter surfaces (Figure 28.1)
- Multiple petechiae present, oozing from umbilical line site noted
- Pupils 4 mm on right, 2 mm on left, trace reactivity
- Left-sided facial weakness, blinks to light on the left but not on the right
- Spontaneous movement of her lower extremities, moves her left upper extremity to tactile stimulation, occasional and minimal movement of the right upper extremity
- Deep tendon reflexes are 2+ throughout but brisker on the left, appendicular hypotonia present

### Laboratory Studies

- White blood cell (WBC) count  $225 \times 10^9/\text{L}$  (70% blasts), hemoglobin 9.2 g/dL, platelets  $110 \times 10^9/\text{L}$
- Prothrombin time 65.1 seconds, partial thromboplastin time 58.6 seconds, international normalized ratio 7.7
- Lactate dehydrogenase 76,000 U/L, uric acid 9.1 mg/dL

## Differential Diagnosis

### Blueberry Muffin Rash (adapted from Holland et al)<sup>1</sup>

#### Extramedullary Hematopoiesis

- Congenital infections: TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex), syphilis, and parvovirus

- Hematologic disease: hemolytic disease of the newborn (Rh, ABO), hereditary spherocytosis

### *Neoplastic Infiltrative Disorders*

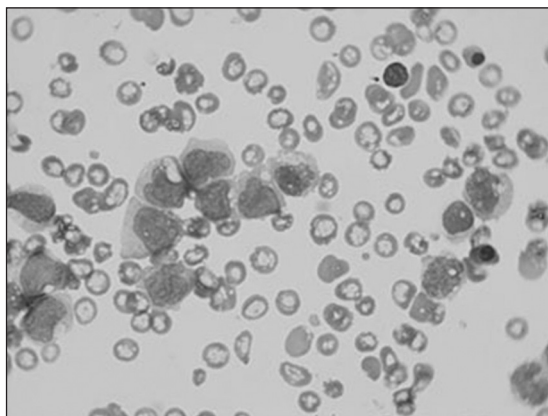
- Congenital leukemia
- Metastatic infiltration: neuroblastoma, rhabdomyosarcoma
- Histiocytosis

### *Vascular Lesions*

- Hemangiomas
- Multifocal lymphangioendotheliomatosis

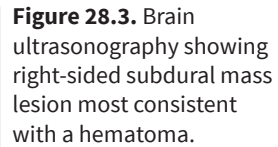
## **Hospital Course**

The infant underwent 2 double-volume exchange transfusions for hyperleukocytosis. Peripheral blood examination revealed multiple blasts (Figure 28.2) that stained positive for myeloperoxidase and  $\alpha$ -naphthyl butyrate esterase.



**Figure 28.2.** Peripheral blood smear stained positive for myeloperoxidase and alpha-naphthyl butyrate esterase; multiple blast cells can be observed.

Flow cytometry showed the blast cells coexpressed cluster of differentiation (CD) 56, CD64, human leukocyte antigen D-related, and CD5 consistent with myeloid progenitor cell lineages. Her chromosomal analysis revealed a *de novo* translocation involving chromosomes 11 and 19, t(11:19), and chromosomal microarray revealed a 533-kilobase deletion on the short arm of chromosome 19 (19p13.11).



**Figure 28.4.** Brain magnetic resonance imaging showing large right-sided subdural hematoma with extensive mass effect and midline shift.

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## Actual Diagnosis

### *Congenital Acute Myeloid Leukemia (AML)*

## The Experts

Congenital leukemia is a rare neonatal disease with an incidence of 4.7 cases per million births.<sup>2</sup> The diagnostic criteria include

- Presentation within the first 4 weeks of age;
- Proliferation of immature myeloid, lymphoid, or erythroid cells;
- Infiltration of immature cells into nonhematopoietic tissues; and
- Absence of other disorders to account for the proliferation.<sup>3,4,5</sup>

Congenital leukemia is more common among male than female (2:1) infants<sup>4</sup> and among Caucasian than (1.6:1) African American infants.<sup>6</sup> Although congenital leukemia represents less than 1% of all childhood leukemias,<sup>2,3</sup> it is more likely to be of myeloid lineage and carries a worse prognosis than childhood leukemias.<sup>7,8,9,10</sup>

Neuroblastoma remains the most common congenital malignancy, but leukemia is the leading cause of death from neoplastic disease in the neonate.<sup>2,11</sup> When detected antenatally, hepatosplenomegaly, hydrops, and polyhydramnios can be seen.<sup>12,13,14</sup> Congenital leukemia is a significant cause of stillbirth.<sup>11,15,16,17</sup>

The most characteristic features of congenital AML are hepatosplenomegaly and leukemia cutis, or infiltration of the dermis and subcutaneous fat with leukemic cells. Lesions are typically firm, violaceous or bluish papules and nodules, but early lesions can be macular.<sup>4</sup>

Additional clinical findings include petechiae and ecchymoses.<sup>18</sup> Respiratory distress may be present secondary to pulmonary hemorrhage from thrombocytopenia or extensive leukemic infiltration and atelectasis.<sup>19,20</sup> A bulging fontanelle may indicate meningeal infiltration or intracranial hemorrhage.<sup>21</sup> At autopsy, more than one-third of neonates have leukemic cells in their cerebrospinal fluid or meninges. Leukemia cutis is more commonly seen in patients with congenital AML (approximately 50%),<sup>18,22</sup> whereas central nervous system (CNS) involvement is more common with congenital acute lymphoblastic leukemia (ALL).<sup>18</sup>

Hematologic findings vary widely, from normal values to profound leukocytosis, anemia, and thrombocytopenia with leukemic blasts frequently detected in the peripheral blood.<sup>7</sup> Leukocytosis may result in hyperviscosity and leukostasis with cardiac, pulmonary, and CNS compromise.<sup>7</sup> Additional laboratory abnormalities include elevated lactate dehydrogenase and uric acid; liver function abnormalities can be seen with extensive hepatic infiltration.<sup>7</sup> The diagnosis typically is confirmed by flow cytometry, skin biopsy, and/or bone marrow aspirate and biopsy.

Congenital leukemia is usually myelogenous in origin, with acute myelomonocytic (M4) and monocytic (M5) the most common subtypes.<sup>18</sup> Translocations involving chromosome 11q23 (*MLL* gene) are detected in approximately half of neonates with AML or ALL. The t(11:19) translocation commonly is seen in males with congenital AML and high white blood counts, as in this patient.<sup>23</sup>

Familial clustering of infant leukemia has not been observed, and predisposing genes have not been identified.<sup>24</sup> In utero intraplacental metastases between concordant twins have been reported.<sup>25,26</sup>

Initial treatment is supportive and may include transfusions to correct anemia, thrombocytopenia, and coagulopathy. Leucopheresis or exchange transfusion may be required for WBC counts over  $100 \times 10^9/L$  or for signs and symptoms of hyperviscosity.<sup>27</sup> Congenital leukemia is nearly universally lethal, with rapid deterioration and death from hemorrhage or infection, if not treated with chemotherapy.<sup>11,28,29,30</sup>

Poor prognostic indicators include high leukocyte count and extramedullary infiltration including the CNS.<sup>18</sup> Spontaneous remission, although rare, has been described for congenital AML.<sup>11,31,32,33,34</sup> In a study of neonates with leukemia (AML and ALL), the overall 3-year survival rate was 26% with a more favorable prognosis for AML (35%) than ALL (9%).<sup>7</sup>

Kathryn Farrell, MD, Robert J. Hayashi, MD, Jennifer A. Wambach, MD, Washington University School of Medicine, St Louis, MO.

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## **A Newborn Who Has a Swollen Upper Extremity**

### **The Case**

A term male newborn presents with a swollen left upper extremity.

#### ***Prenatal History***

35-year-old gravida 2 para 1001 Caucasian mother

Estimated gestational age: 38 1/7 weeks

Uneventful pregnancy; ultrasonography at 22 weeks' gestation did not reveal any problems

Blood type A+, rapid plasma reagin nonreactive, hepatitis B surface antigen negative, rubella immune, group B Streptococcus screen negative

Spontaneous rupture of membranes at 9 hours prior to delivery and amniotic fluid was clear

#### ***Birth History and Presentation***

The infant was delivered from vertex presentation by spontaneous vaginal delivery. A pediatric team was not present at the delivery because there were no risk factors. Delivery was complicated by left shoulder dystocia. Because the labor and delivery nurse noted that the infant had poor tone and respiratory effort, he received positive pressure ventilation with bag and mask for approximately 1 minute, and the pediatric team was called. Apgar scores were 3 at 1 minute and 7 at 5 minutes. The birth-weight was 3.7 kg.

What other physical examination findings are pertinent?

What laboratory tests would you order?

What interventions are indicated?



## **Case Progression**

### ***Vital Signs***

Heart rate, 120 beats/min

Respiratory rate, 44 breaths/min

Blood pressure, 58/32 mm Hg

Temperature, 98.6°F (37°C)

### ***Physical Examination***

Head: Normal, open fontanelles; no dysmorphic facial features; intact palate; patent nares

Lungs: Clear; equal breath sounds

Cardiovascular Examination: Normal S1, S2; regular rhythm; no murmur; equal peripheral pulses; capillary refill time, 3 seconds

Abdomen: Soft; liver is 1 cm below the right costal margin; spleen is not palpable; three-vessel umbilical cord

Genitourinary Examination: Normal male

Extremities: Normal, except the left arm is enlarged from wrist to shoulder, reddish, and firm to palpation (Figure 29.1)

Neurologic Examination: Decreased movement of the left arm; left hand grasp intact

Skin: Generally pale except for the left arm; petechiae are noted increasingly over the chest, abdomen, and groin (Figure 29.2)



**Figure 29.1.** Newborn with enlarged left arm.



**Figure 29-2.** Pale newborn with generalized petechiae and enlarged left arm.

The patient was started on oxygen by nasal cannula at 0.1 L/min at 1.0 FiO<sub>2</sub>. Umbilical arterial and venous lines were placed, and a normal saline bolus was administered. The patient received intravenous vitamin K. Results of the laboratory evaluation included

- Hematocrit, 33% (0.33)
- Platelet count,  $23 \times 10^3/\text{mcL}$  ( $23 \times 10^9/\text{L}$ )
- Abnormal coagulation profile, including international normalized ratio of 2.8
- Metabolic acidosis with base deficit of -11 mEq/L

Subsequently, the patient received platelets, fresh frozen plasma, and packed red blood cells and was prepared for transport to a referral center.

## ***Differential Diagnosis***

### ***Term Infant Presenting With Swollen Left Arm***

Arteriovenous malformation

Giant hemangioma

Tourniquet syndrome

Neuroblastoma

Humerus fracture

What phenomenon is causing the petechiae and coagulopathy?

**Take a moment to consider the diagnosis in this infant.**

## Actual Diagnosis

### *Giant Hemangioma With Kasabach-Merritt Phenomenon*

Plain radiography of the arm revealed no fractures (Figure 29.3). Consultation with hematology and plastic surgery services concluded that the patient had a giant left arm hemangioma with evidence of a consumptive coagulopathy consistent with Kasabach-Merritt phenomenon without compartment syndrome. Echocardiography revealed good cardiac function, and head ultrasonography findings were normal.



**Figure 29.3.** Plain radiograph of newborn's left arm without any evidence of fracture.

Soon after arrival at the referral center, the infant was started on methylprednisolone at 3 mg/kg per day. An elastic bandage was wrapped around his arm to provide compression and removed intermittently for assessment of the affected area. The infant continued to require blood product transfusions, including platelets, packed red blood cells, and cryoprecipitate. Initial goals included a platelet count greater than  $50 \times 10^3/\text{mcL}$  ( $50 \times 10^9/\text{L}$ ), hematocrit greater than 30% (0.30), and fibrinogen greater than 100 to 150 mg/dL (1.0 to 1.5 g/L). Despite these interventions, the infant's arm continued to appear to enlarge. Daily interferon-alpha-2b therapy was initiated 9 days after delivery, steroid therapy was continued, and aminocaproic acid was begun.

Due to the persistent need for transfusions, a more permanent internal jugular central line was placed 11 days after delivery. Magnetic resonance angiography at 13 days after delivery confirmed the presence of a hemangioma involving the left arm only, from the axilla to just past the elbow, and not extending into the chest.

Over the course of his continued hospitalization, his arm decreased in size gradually, as did his transfusion need. His last platelet transfusion was administered approximately 3.5 weeks after delivery, and the last cryoprecipitate transfusion was provided 5 weeks after delivery. As his condition improved, his steroid dosing was weaned, and the interferon was decreased to every-other-day administration. He was discharged home 6 weeks after delivery on prednisolone 1 mg/kg per day, interferon every other day, and aminocaproic acid.

## The Experts

Hemangiomas are the most common infant soft-tissue tumor, occurring in 5% to 10% of 1-year-old children.<sup>1</sup> Traditionally, the term hemangiomas applied to a variety of vascular lesions. Although different types of lesions may appear similar, they may exhibit different growth patterns, responses to treatment, and even prognoses. Hemangiomas are characterized by three distinct phases: proliferative, spontaneous involution, and resolution. A biologic reclassification for vascular birthmarks was proposed in 1982 based on clinical manifestations, histopathologic features, and natural history. Today, such lesions are divided into two categories: hemangiomas and vascular malformations.

Hemangiomas are vascular tumors with the classic presentation of a growth phase marked by endothelial proliferation and hypercellularity, a spontaneous involution phase, and ultimately, resolution. Among the known vascular tumors of infancy are hemangiopericytomas, pyogenic granulomas, tufted angiomas, and kaposiform hemangioendotheliomas. In contrast, vascular malformations are structural anomalies derived from capillaries, veins, lymph vessels, arteries, or a combination of all these. One example is arteriovenous malformation.

The clinical manifestations of hemangiomas vary substantially; they can be found at different depths, locations, and stages of evolution. In the newborn, they often present as pale macules with telangiectasis. Eventually, they become bright red and slightly elevated. If superficial, they can be identified as noncompressible plaques. When found deeper in the skin, hemangiomas are soft, warm masses that have a slight bluish color. Frequently, they have both superficial and deep components and range from a few millimeters to several centimeters in diameter. Usually they are solitary, but up to 20% of affected infants have multiple lesions. Females are 3 times

more likely to have hemangiomas, and the incidence is increased in preterm infants. Some 55% of hemangiomas present at birth, with the remainder developing in the first postnatal weeks.<sup>1</sup>

It is difficult to predict the duration of the proliferative phase of hemangiomas. Superficial hemangiomas reach maximal size in 6 to 8 months; deep hemangiomas may reach a maximum size at 12 to 14 months. The onset of involution frequently is even more difficult to predict. Some hemangiomas change from bright red to purple or gray before involution. Large facial hemangiomas can leave disfiguring scars when they resolve.<sup>1</sup>

Imaging studies can aid in diagnosing hemangiomas. The diagnosis is less clear if large congenital lesions and hepatic lesions are present, and the differential diagnosis includes neuroblastoma, leukemia, and even hepatoblastoma. Doppler ultrasonography reveals characteristic flow patterns that differ from those seen with solid tumors and vascular malformations. Computed tomography scans show a homogeneous mass with large feeding vessels and intense and persistent contrast enhancement. Magnetic resonance imaging demonstrates well-circumscribed, densely lobulated masses that have a specific signal intensity.<sup>1</sup>

Several complications can arise from large or multiple hemangiomas. Cutaneous hemangiomas can cause functional compromise or permanent disfigurement. Ulceration can be excruciatingly painful and places the infant at risk of infection, hemorrhage, and scarring. (The ulceration usually is preceded by pain from possible ischemia and necrosis during involution and can manifest in infants as irritability, decreased feeding, and inability to sleep).<sup>1</sup> Other complications include high-output cardiac failure and Kasabach-Merritt syndrome or phenomenon.

The management of hemangiomas is surrounded by controversy. Some experts argue for treatment of all affected patients; others support watchful waiting if there are no active complications. Even if no specific therapy is started, active emotional support should be provided to parents who may be shocked by having a newborn who has such a large lesion.<sup>1</sup>

Therapeutic options depend on hemangioma size and location as well as the practitioner. Among the modalities that have been used are irradiation (very rare today), excisional surgery (very difficult with vascular lesions), corticosteroids (systemic versus intralesional, high-dose versus low-dose), interferon-alpha (2a versus 2b), lasers (pulsed dye versus continuous wave), cryotherapy (tried mostly in Europe and South America), embolization, and even angiogenesis inhibitors.

## **Kasabach-Merritt Syndrome**

Kasabach-Merritt syndrome (KMS) was first described in 1940.<sup>2</sup> Kasabach and Merritt noted the association of thrombocytopenic purpura with the presence of a rapidly enlarging capillary hemangioma in a newborn male. They treated the infant with red blood cell transfusions, deep roentgen treatments, and radium for nearly 3 months, and the baby survived. Kasabach-Merritt syndrome is a complication of rapidly enlarging vascular lesions, and the classic triad includes hemolytic anemia, thrombocytopenia, and coagulopathy. As with hemangiomas, treatment remains controversial.

Kasabach-Merritt syndrome occurs very rarely (<0.5% of patients who have hemangiomas), and neither size nor site of the hemangioma can predict the development of KMS. When KMS does occur, there is a 30% to 40% mortality rate.<sup>3</sup> The pathogenesis is unclear, although there has been much speculation. Some experts question whether the proliferation of the hemangioma itself is the cause or whether a proliferative rate develops above a certain threshold.<sup>4</sup> The pathophysiology has been presumed to be from platelet trapping by abnormally proliferating endothelium within the hemangioma,<sup>5</sup> which results in platelet activation and secondary consumption of clotting factors. The thrombocytopenia can be profound ( $<20 \times 10^3/\text{mcL}$  [ $20 \times 10^9/\text{L}$ ]), and the half-life of platelets in KMS is shortened to 1 to 24 hours.<sup>6</sup> It also is speculated that exposure and adhesion of platelets to subendothelium or abnormal endothelium in hemangiomas might result in platelet aggregation and activation. Excessive flow and shear rates contribute to this process, leading to a cycle of continued consumption of platelets and clotting factors, eventually initiating fibrinolysis and the observed coagulopathy.<sup>4</sup>

Kasabach-Merritt syndrome is diagnosed clinically in newborns who have red cell fragmentation (hemolytic anemia), thrombocytopenia, and coagulopathy. Often, hemangiomas are present on the skin surface, but sometimes occult/visceral hemangiomas are found after searching for them in newborns who exhibit anemia, thrombocytopenia, and coagulopathy. Although the goals of KMS management are straightforward, achieving them is not. First, the patient must be supported and stabilized, and second, the hemangioma(s) must be removed or ablated.

Stabilization is accomplished with blood products (packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate, if needed). Eradication of the inciting hemangioma(s) usually proves much more difficult, with many different approaches having been tried throughout the years. Treatment has ranged from radiotherapy (no longer used, because of growth malformation, except for extreme emergencies), surgery (excision for single cutaneous lesions, splenectomy for multiple splenic lesions, wedge resection/hepatectomy for liver lesions, wide local excision, or amputation), steroid therapy, compression therapy (particularly useful for limb involvement and often used as adjuvant therapy in medical management), vascular

embolization (can be used for lesions that have easily identifiable feeder vessels), gel foam, polyvinyl alcohol, and metal coils. More recent approaches have included interferon-alpha therapy (both 2a and 2b), chemotherapy (usually weekly vincristine), antithrombin III, antiplatelet agents (ticlopidine, pentoxifylline), antifibrinolytic agents (aminocaproic acid, tranexamic acid [some success in combination with other agents; should be used when fibrinolysis is the primary component of coagulopathy]), and laser therapy (used in rapidly proliferating superficial cutaneous hemangiomas, especially those that ulcerate). Therapies currently in development and being tested include both antiangiogenic agents and pegylated recombinant human megakaryocyte growth and development factor (Peg-rHuMGDF).

Although there is still disagreement, most experts begin treatment with corticosteroids at a dosage of 2 to 5 mg/kg per day. The expectation is that 30% of children will respond to prednisone therapy, 40% will respond equivocally, and 30% will fail to respond.<sup>7</sup> Unfortunately, no information can suggest which patient will respond to steroids. Higher “megadose” therapy of 30 mg/kg per day of prednisolone for 3 days, with weaning over 4 to 5 weeks, has achieved some success,<sup>8,9</sup> although this approach remains controversial.

If there is no response to steroids after 1 to 2 weeks, the dose is increased or an alternative therapy recommended.<sup>4</sup> The second-line therapy often is interferon-alpha (2a/2b), whose mechanism of action probably is as an antiproliferative/antiangiogenic agent. Its use has been associated with a reduction in urinary excretion of angiogenic basic fibroblast growth factor (bFGF), which may indicate an inhibition of bFGF-induced angiogenesis.<sup>10</sup> The onset of action of interferon-alpha is slower than that of steroids, and the standard dose is 3 million units/m<sup>2</sup> per day. As many as 50% of treated patients may respond, usually within 1 week to 2 months.<sup>11</sup> Concurrent therapy has made it difficult to determine if interferon-alpha contributes to the disappearance of the hemangioma or if normal spontaneous involution has occurred. Recent reports of spastic diplegia, which is estimated to occur in 2% to 20% of infants receiving interferon-alpha (both 2a and 2b), are concerning.<sup>12,13,14,15,16</sup>

Although steroids and interferon-alpha are usually considered first- and second-line therapy, some institutions treat patients initially with the chemotherapeutic agent vincristine.<sup>17</sup> Others have used vincristine as second-line therapy for steroid nonresponders.<sup>7,18</sup> Ultimately, the adverse effect profile of chemotherapeutic drugs must be weighed against the risk of death in KMS. Some of the complications from vincristine include abdominal pain, transient loss of deep tendon reflexes, and irritability. Most experts agree that vincristine is usually considered safe and sometimes effective. In practice, when treating KMS, most experts choose the treatment modality with which they have the most experience and comfort.

*Joshua Schiffman, MD, Henry C. Lee, MD, Stanford University Medical Center, Stanford, CA*

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**COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER**

In 2008 (after this case was published), propranolol was found to be beneficial in the management of neonatal hemangiomas, and it is associated with fewer side effects compared to steroids, interferon-alpha, or vincristine treatment.<sup>1</sup> There are only a few reports about propranolol use in patients with KMS, and at present, it is uncertain if there is a role for this agent as monotherapy, in combination with other medications, or as a maintenance therapy.<sup>2</sup>

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## Twins With Persistent Jaundice

### Presentation

A pair of twin sisters in the nursery remain persistently jaundiced at 1 month of age. The dichorionic diamniotic twins were born at 32 weeks' gestation to a 29-year-old Asian woman. This was her third pregnancy, and she has a 1½-year-old daughter at home. The pregnancy and delivery were uncomplicated, with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, for the twins. Twin A weighed 1,333 g, and twin B weighed 1,469 g. The initial course for these appropriately grown twins was unremarkable, except for some respiratory distress requiring nasal cannula supplemental oxygen, thermoregulation in an isolette, gavage feedings with human milk, and apnea and bradycardia treated successfully with caffeine. They now are in cribs, receiving human milk exclusively, and otherwise well.

The mother's blood type is O Rh-positive, and the babies' blood type is B Rh-positive. Results of a direct Coombs test are negative. Serum bilirubin profile, hemoglobin, and phototherapy treatment for one of the twins are outlined in Table 30.1; the profile is similar for both twins. Physical examination yields unremarkable findings except for jaundice. Both infants are growing along the 25th to 50th percentile for weight and occipitofrontal circumference. No hepatosplenomegaly or pallor is noted. An additional piece of history guides the diagnosis and prevents expensive evaluation.

*Take a moment to consider the diagnosis in this infant.*

**Table 30.1.** Profile for One Twin

Age (days)	Serum Bilirubin (mg %)	Hemoglobin (g/dL) (g/L)
2	6.5	15.0 (150)
3	8.7 (PT)	
4	4.5 (PT stopped)	
5	3.1	
19	10.9	
25	13.0 (PT started)	11.8 (118)
26	10 (PT stopped)	
27	7	
30	9.9	

PT=phototherapy; bilirubin predominantly indirect

## ***The Diagnosis***

A history of prolonged jaundice in the older sibling while breastfeeding strengthened the suspicions of human milk jaundice. She had remained jaundiced for 3 months and is developmentally normal.

### ***Prolonged Jaundice***

Jaundice (serum bilirubin  $>10$  mg%) beyond 2 weeks in a term or a preterm neonate is defined as prolonged jaundice and demands evaluation. The causes and evaluation are different for indirect and direct hyperbilirubinemia.

Parenteral nutrition; sepsis, including urosepsis; and anatomic abnormalities of the intra- and extrahepatic biliary tract (biliary atresia) cause direct bilirubinemia. Jaundice caused by parenteral nutrition is diagnosed by history. Urosepsis causing jaundice is diagnosed by blood and urine culture. Abdominal ultrasonography, radioisotope scanning, and liver biopsy are used for diagnosing anatomic abnormalities. Congenital intrauterine infection is suspected in small-for-gestational age babies who have hepatosplenomegaly, microcephaly, chorioretinitis, and intracerebral calcifications in varying combinations.

Indirect hyperbilirubinemia can be due to hemolytic and nonhemolytic disorders. Blood group incompatibility, structural abnormalities of the red cell membrane, red cell enzymatic defects, and disorders of hemoglobin synthesis are causes of hemolytic anemia and hemolytic jaundice.

Congenital hypothyroidism, galactosemia, bowel obstruction, constipation, and human milk jaundice are examples of nonhemolytic causes of indirect hyperbilirubinemia. Crigler-Najjar syndrome is a rare variety of nonhemolytic unconjugated hyperbilirubinemia.

The twins in this case had indirect hyperbilirubinemia. Stable hemoglobin values, absence of hepatosplenomegaly, and appropriate reticulocytosis (6% at 1 month of age) made hemolytic anemia and hemolytic jaundice unlikely. A normal peripheral smear, obtained as part of a routine complete blood count, did not reveal abnormal red cell morphology. The state screen results were normal, ruling out galactosemia and hypothyroidism. The family history of human milk jaundice and absence of hemolytic disorders in the family (especially due to their Asian descent) pointed to the diagnosis of human milk jaundice. No confirmatory test can prove the diagnosis, but a trial off human milk on day 32 provided typical results (Table 30.2).

**Table 30.2. Laboratory Values During Trial off Human Milk**

Age (days)	Serum Bilirubin (mg %)
32	11.4 (human milk stopped, no PT)
35	7.5 (human milk restarted)
37	7.3

PT=phototherapy

### ***The Condition***

Human milk jaundice, initially described by Arias and associates in 1963,<sup>1</sup> is a poorly understood condition. Postulated mechanisms include

The presence of a lipoprotein lipase in human milk that releases free fatty acids, which inhibit glucuronyl transferase enzyme activity.

Progesterone metabolite in the milk (5 beta-pregnane-3 alpha, 20 beta-diol, and other pregnanediols), which inhibits glucuronyl transferase enzyme activity.

Increased beta-glucuronidase activity in human milk, leading to increased conversion of bilirubin diglucuronide to monoglucuronide and subsequent reabsorption and enterohepatic circulation of bilirubin.

Defects of the *UGT1A1* gene, with one or more components in the milk possibly triggering the jaundice in infants who have such mutations. The mutations described are identical to those detected in patients who have Gilbert syndrome.

None of the mechanisms has been demonstrated consistently, and conflicting findings between in vivo observations and in vitro experiments have prevented clarification of the pathogenesis.<sup>1</sup>

Cessation of breastfeeding resulting in a decline in the serum bilirubin values, with rebound after reintroduction of human milk, was demonstrated in 1963 by Newman and Gross.<sup>2</sup> The rebound generally does not lead to bilirubin concentrations noted before cessation of human milk feeding. No long-term neurodevelopmental effects result from human milk jaundice.

Human milk jaundice differs from jaundice associated with breastfeeding or early breastfeeding jaundice.<sup>3</sup> During the period that first-time breastfeeding mothers establish their milk supply, intake in their exclusively breastfed infants may be insufficient. The infants become dehydrated, lose weight, are constipated, develop jaundice, and may develop hyponatremia. Encouraging breastfeeding while supplementing with formula for a limited time resolves the jaundice. Phototherapy and intravenous fluids may be needed, depending on the serum bilirubin value and severity of dehydration. American Academy of Pediatrics guidelines for phototherapy should be reviewed to decide on the indication for phototherapy.<sup>4</sup> Follow-up evaluation of breastfed babies after discharge by their primary pediatricians is recommended to recognize and institute appropriate management of this complication of breastfeeding.

### **Lesson for the Clinician**

Human milk jaundice is a diagnosis of exclusion, but a history of a similar affliction in siblings and lack of hemolytic disorders in the family can be reasonable indicators of the diagnosis and help avoid expensive evaluation.

*Akshaya J. Vachharajani, MD, Department of Pediatrics, Division of Newborn Medicine, Washington University in St Louis and St Louis Children's Hospital, St Louis, MO*

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*Part 8*

# **Inborn Errors of Metabolism**

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## **Persistent Severe Metabolic Acidosis in a Newborn**

### **Presentation**

A female preterm infant was born at 28 weeks' gestation to a G3P2A1 woman (third-degree consanguineous marriage) by emergency cesarean delivery due to severe fetal growth restriction, oligohydramnios, and increasing liver transaminase levels in the mother. First conception was miscarriage at 12 weeks' gestation. The second conception was intrauterine fetal demise at 30 weeks' gestation; the pregnancy was complicated with acute fatty liver of pregnancy (AFLP) and acute kidney injury. Placenta showed massive perivillous fibrin deposition. Present pregnancy was spontaneously conceived. Prepregnancy, mother was diagnosed as hypothyroid and was started on thyroxine. She had also been started on aspirin since the last pregnancy and had received a complete course of antenatal steroids at 27 weeks' gestation. Blood pressure of the mother at the time of admission was 140/90 mm Hg. This pregnancy was also complicated with AFLP, with serum glutamic-pyruvic transaminase levels of 586 U/L and lactate dehydrogenase levels of 863 U/L. The infant at birth weighed 960 g, required resuscitation with bag and mask for 30 seconds, and had Apgar scores of 5 and 7 at 1 minute and 5 minutes, respectively. Immediately after resuscitation, the infant was noted to have respiratory distress (Silverman-Andersen score of 8 of 10). In view of this distress, the infant was shifted to the neonatal intensive care unit on a T-piece resuscitator and was started on continuous positive airway pressure at 15 minutes of age with a positive end-expiratory pressure of 5 cm and fraction of inspired oxygen of 0.50. Chest radiograph revealed surfactant deficiency. Intubation, surfactant administration, and extubation was given at 2 and 6 hours after birth in view of persistent respiratory distress and increased fraction of inspired oxygen requirement, respectively. She also had poor circulation, was off-color, and had increased capillary perfusion starting from 2 hours after birth. This shock was initially managed with a fluid bolus, then with increasing inotropic support of dopamine and dobutamine. Blood gas analysis revealed persistent metabolic acidosis (Table 31.1), which did not respond to fluids, inotropes, packed



**Table 31.1. Blood Gas Analysis With Anion Gap With Respect to Hours After Birth**

Hours	6	10	17	22	30	36	51	62	70	74
pH	7.006	7.061	7.107	7.17	6.962	7.014	7.00	7.23	7.121	7.106
PCO <sub>2</sub> , mm Hg	66.3	47.1	32.4	41.5	59.8	28.3	84.5	21.3	39	40.1
PO <sub>2</sub> , mm Hg	43	50	58	48	50	60	67	73	71	49
Base excess (BE)	−15	−17	−19	−13	−18	−24	−10	−18	−16	−17
HCO <sub>3</sub> , mEq/L	16.6	13.3	10.2	15.2	13.5	7.2	20.9	9.1	12.9	12.6
Na <sup>+</sup> , mEq/L	137	136	140		139	138	143	140		154
K <sup>+</sup> , mEq/L	5.9	6.1	5.7		6.5	6.3	5.9	6.8		8.5
Cl <sup>−</sup> , mEq/L					105			102		110
Anion gap					20.5			28.9		31.4

cell transfusion, ventilation, sodium bicarbonate infusion, or (lastly) exchange transfusion. The infant was started on mechanical ventilation at 6 hours after birth and then on high-frequency oscillation for persistent respiratory distress, shock, and metabolic/respiratory acidosis.

Over the first 4 days after birth, the infant had progressive illness complicated with shock, patent ductus arteriosus, renal failure, seizures, and persistent metabolic acidosis. The infant experienced multiorgan dysfunction and died 87 hours after birth. Investigations revealed the following: total white blood cell counts (2 hours), 25,300/mm<sup>3</sup>; platelets (2 hours), 2.6 lakh/mm<sup>3</sup>; C-reactive protein (22 hours), 0.6 mg/dL; blood sugar levels (2 hours), 54 to 146 mg/dL; hematocrit (2 hours), 41.3% to 28.4% (10 hours); blood urea (31 hours), 121 mg/dL; creatinine (31 hours), 1.8 to 2.3 (58 hours) mg/dL; potassium (6 hours), 5.9 to 8.5 (74 hours) mEq/L; ammonia (21 hours), 120.1 mcmol/L; serum lactate (67 hours), 15.8 mmol/L; and cerebrospinal fluid (CSF) lactate (70 hours), 16.1 mEq/L. Ultrasound of the kidneys and urine ketone levels were normal. Cranial ultrasonography at 76 hours after birth revealed bilateral grade II intraventricular hemorrhage. Results of blood cultures were sterile. Reports of one investigation performed during the illness confirmed the diagnosis.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

Persistent metabolic acidosis in a preterm extremely low-birthweight infant could occur due to shock, hypoxia, anemia, increased work of breathing, sepsis, and inborn errors of metabolism. In the index newborn, when all measures to improve acidosis failed, a strong possibility of inborn error of metabolism was considered. Because the anion gap was increased and lactate levels were high, primary lactic acidosis was the first possibility. Normal CSF lactate levels negated this diagnosis. Newborn screening was also negative for organic acids. Persistent metabolic acidosis, increased anion gap, and negative urine ketones lead us to the clinical possibility of fatty acid oxidation defect. History of AFLP in the mother, hyperammonemia, normal CSF lactate, absent urine organic acids, and acylcarnitine profile confirmed the diagnosis of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency. The acylcarnitine profile revealed a marked elevation of hydroxyhexadecanoylcarnitine (C16OH), 2.94 (0.02–0.11 mcmol/L); elevated hydroxytetradecenoylcarnitine (C14OH), 0.30 (0.02–0.11 mcmol/L); elevated hydroxyhexadecenoylcarnitine (C16:1OH), 0.51 (0.04–0.16 mcmol/L); elevated hydroxyoctadecenoylcarnitine (C18:1OH), 0.30 (0.02–0.10 mcmol/L); and marked elevation of the related LCHAD ratio, 13.5 (0.23–0.79), consistent with diagnosis of fatty acid oxidation defect (LCHAD deficiency). There are three different forms of presentation: (1) the severe neonatal type, which is universally fatal with cardiac involvement; (2) the infancy onset hepatic form; and (3) a milder, late-onset type with a neuromyopathic phenotype. The age of onset varies from neonate to several years of age, with a mean age

at presentation of 5.8 months. Fifteen percent of cases may present in the neonatal period.<sup>1</sup> In the indexed case, the infant had the severe neonatal form, which led to her having a turbulent course in the nursery with refractory shock that did not respond to high doses of inotropes and steroids, and she died of multiorgan dysfunction, including renal failure and pulmonary hemorrhage.

## ***The Condition***

Very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCAD deficiency) is a condition that prevents the body from converting certain fats to energy, particularly during periods without food (fasting). Very long-chain acyl-coenzyme A dehydrogenase deficiency is estimated to affect 1 in 40,000 to 120,000 people. This condition is inherited in an autosomal recessive pattern (2p23.3), which means both copies of the gene in each cell have mutations. The parents of an individual who has an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Very long-chain acyl-coenzyme A dehydrogenase deficiency was first discovered in 1992, and clinical experience with VLCAD deficiency has been accumulating rapidly.<sup>2,3</sup> Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase is one of three enzymatic activities that comprise the trifunctional protein of the inner mitochondrial membrane. Patients who have LCHAD deficiency activity usually present at a median age of 6 months. A minority of patients (up to 15%) may present during the neonatal period. Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency in a fetus predisposes the mother to the gestational complications of hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome) and AFLP. Patients usually present with hypoketotic hypoglycemia, cardiomyopathy, hypotonia, and hepatomegaly. These metabolic crises occur more frequently in infancy and early childhood. Some patients present with peripheral sensorimotor polyneuropathy, myoglobinuria, and progressive visual loss. Rarely, affected infants can present with acute cholestasis jaundice or massive total hepatic necrosis in infancy.<sup>1</sup> A molecular defect that affects the mitochondrial trifunctional protein causes LCHAD deficiency activity. In LCHAD deficiency, most of the patients are homozygous for a guanine to cytosine transversion at position 1528, involving the alpha subunit of the mitochondrial trifunctional protein in the active site domain of the LCHAD activity encoding region. Diagnosis of LCHAD deficiency is suggested by demonstrating increased secretion of 3-hydroxydicarboxylic acids in urine by using gas chromatography–mass spectrometry or by demonstrating accumulation of 3-hydroxyacyl-carnitines as measured by using tandem-mass spectrometry in plasma.<sup>4</sup> Confirmation of the diagnosis is possible by measuring LCHAD activity in lymphocytes, fibroblasts, or muscle or liver biopsies<sup>5</sup> and according to mutational analysis. In the majority of LCHAD-deficient patients, at least one allele carries this point mutation (1528 G>C).<sup>6</sup> The treatment of affected patients is directed at the avoidance of fasting. Most patients are provided with uncooked cornstarch and medium-chain

triglyceride oil supplementation to further decrease exposure to fasting. Oral supplementation with docosahexaenoic acid ethyl ester may be considered to improve visual function. Carnitine supplementation is given if there is hypocarnitinemia, and it is avoided during acute episodes because there is a risk of arrhythmias.<sup>7</sup>

### Lessons for the Clinician

Inborn errors of metabolism must be considered in all newborns presenting with persistent metabolic acidosis.

Persistent metabolic acidosis with increased anion gap and negative urine ketones along with maternal AFLP or maternal HELLP syndrome suggest the possibility of fatty acid oxidation defects.

Deepak Sharma, MD, DNB Neonatology (student), Srinivas Murki, MD, DM Neonatology, Oleti Tejopratap, MD, DM Neonatology, Vasikarla Madhavi, MD, Fellowship in Fetal Genetics, Fernandez Hospital, Hyderabad, Andhra Pradesh, India

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### COMMENT BY DR JOSEF NEU, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE

Note the similarities between this case and Case 32.

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## **Lethargy in a 5-Day-Old Boy**

### **Presentation**

A 5-day-old boy arrives at the clinic for his first postnatal visit. His parents report a 2-day history of increased sleepiness and reluctance to feed.

The infant was delivered at 38 weeks' gestation by repeat cesarean section for oligohydramnios. His birthweight was 6 lb, 8 oz, and Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. The nursery stay was uneventful, and mother and child were discharged after 2 days.

On physical examination today, the infant is lethargic, hypotonic, and clinically dehydrated. His temperature is 34°C, heart rate is 120 beats/min, respiratory rate is 60 breaths/min, oxygen saturation is 93% to 96% in room air, and glucose measures 73 mg/dL (4.1 mmol/L). Intravenous fluids are started during transport to the pediatric emergency department. On arrival, intubation and ventilatory support are required following two seizure episodes and bradycardia. After a full sepsis evaluation, antibiotics and a dopamine drip are begun in the intensive care unit. As pertinent laboratory values are reviewed, the diagnosis becomes clear.

### **Discussion**

Assessment of the infant's electrolytes indicated several metabolic derangements:

Sodium, 160 mEq/L (160 mmol/L)

Potassium, 7.2 mEq/L (7.2 mmol/L)

Chloride, 128 mEq/L (128 mmol/L)

Carbon dioxide, less than 5 mEq/L (5 mmol/L)

Anion gap, 27 mEq/L (27 mmol/L)

Arterial blood gas showed a pH of 6.98,  $\text{PCO}_2$  of 13 mm Hg,  $\text{PO}_2$  of 163 mm Hg, and bicarbonate of 3.0 mEq/L (3.0 mmol/L). Serum ammonia measured 2,348 mcg/dL (1,676  $\mu\text{mol/L}$ ).

*Take a moment to consider the diagnosis in this infant.*

An inborn error of metabolism was diagnosed, and consultation with a metabolic specialist facilitated transfer to a tertiary care center, where a definitive determination of methylmalonicacidemia was made.

## **The Diagnosis**

Whenever a neonate presents in extremis, sepsis must always be considered. However, when laboratory values indicate hyperammonemia, acidosis, and an increased anion gap, an inborn error of metabolism is the likely cause. Although newborns are generally screened for metabolic defects, the results of such testing may become available only after a potentially life-threatening event occurs, as in this case.

Inborn errors include amino acid disorders, organic acidemias, and urea cycle defects. Critical to making the diagnosis is a strong index of suspicion plus serum ammonia, pH, and carbon dioxide measurements. High ammonia values with a normal anion gap and pH indicate a urea cycle defect, and increased ammonia with a large anion gap suggests organic acidemia. Confirmatory tests in this patient included acylcarnitine profile and assessment of urine for organic acids and serum homocysteine.

## **The Condition**

Although MMA can result from cobalamin deficiency, it is most commonly an autosomal recessive defect that has a prevalence of 1 in 48,000. Multiple mutations on chromosome 6p12 have been described, and new mutations continue to be identified. Catabolic stress such as febrile illness or ingestion of a high-protein diet can precipitate acute metabolic decompensation. There are two forms: the neonatal (as in this case) and a more indolent infantile form. In the infantile form, the child presents with failure to thrive and hypotonia. Dysmorphic features and neurologic and other organ involvement may be seen. Classic facial features include a triangular mouth and high forehead. Neurologic complications include seizures and psychomotor and developmental delays. Pancreatitis, fatty liver, cardiomyopathy, and interstitial nephritis are also associated with the infantile form of the condition.

## **Treatment**

The mainstay of management is the immediate recognition and treatment of acute episodes of decompensation. Parents should be attuned to symptoms in their child and act quickly. Clinicians should not hesitate to treat by using online protocols and

consulting a specialist. The potential for cerebral edema due to elevated organic acids and ammonia should always be considered before a lumbar puncture is performed.

Use of lactated Ringers to correct dehydration in a suspected metabolic disorder should be avoided. Bicarbonate may be given slowly if the pH is less than 7.22 or the serum bicarbonate is less than 14 mEq/L (14 mmol/L). Hypoglycemia should also be corrected. Increasing total calories by 20%, preferably with glucose, can avoid a catabolic state. Elimination of any toxic substances should be facilitated by treating constipation, if present, and eradicating bacterial flora with antibiotics. Supplementation with L-carnitine remains controversial but has demonstrated effectiveness in some reports. Insulin, a potent anabolic agent, has been proposed as adjunctive therapy, although its efficacy in reversing the catabolic state has not been substantiated. In severe cases involving intractable acidosis, hyperammonemia, or coma, hemodialysis may be necessary.

### **Lessons for the Clinician**

Inborn errors of metabolism should be suspected when a newborn presents with a severe acute illness and in older infants who have failure to thrive and developmental delays. Serum ammonia, pH, and carbon dioxide values aid in the diagnosis. Urgent recognition and treatment of acute metabolic decompensation in conjunction with a metabolic specialist is necessary.

Milena Osorio, MD, Roseann T. Spiotta, MD, FAAP, Albert Einstein College of Medicine/Jamaica Hospital Medical Center Family Medicine Residency Program, Jamaica, NY

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### **COMMENT BY DR JOSEF NEU, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE**

Note the similarities between this case and Case 31.



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## Two-Day-Old With Hypothermia and Hypoglycemia

### Presentation

A 2,160-g term female is born to a 24-year-old G2P0010 mother. Pregnancy complications include iron deficiency anemia; intrauterine growth restriction diagnosed by using a prenatal ultrasound during the third trimester; positive serologic result for maternal herpes simplex, with no active lesions present at delivery; and vaginal culture positive for group B Streptococcus. All other serologic test results were unremarkable. Before delivery, the mother received valacyclovir and multiple doses of penicillin. The infant was born at a community hospital via induced vaginal delivery due to intrauterine growth restriction status, without prolonged rupture of membranes. Apgar scores are 9 and 9 at 1 and 5 minutes, respectively. Physical examination at birth demonstrates the infant is small for gestational age but is otherwise within normal limits. Weight at birth is 2,160 g, and length is 43.2 centimeters, both below the third percentile for gestational age and gender. Head circumference is 33.5 centimeters (15th percentile).

On day 2, just before discharge, the infant is noted to be hypothermic (93°F) and hypoglycemic. She is transferred to the neonatal intensive care unit (NICU) of the community hospital and undergoes a partial sepsis evaluation, including blood, urine, and surface viral cultures. Presumptive treatment for clinical sepsis is initiated with ampicillin, gentamicin, and acyclovir. Subsequently, the infant is noted to have evidence of respiratory distress and requires continuous positive airway pressure support. An arterial blood gas sample is obtained, with the following results: pH, 7.1; PCO<sub>2</sub>, 9 mm Hg; bicarbonate, 7 mmol/L; and base excess, −25 mmol/L. She receives a 2-mEq/kg sodium bicarbonate bolus, and a repeat arterial blood gas sample shows a pH of 7.3, PCO<sub>2</sub> of 15 mm Hg, and base excess of −20 mmol/L. Lactate levels are within normal limits, but ammonia levels are elevated to >400 mcmmol/L, and 3 hours later they increase to >600 mcmmol/L. Anion gap is 27. Results of the urinalysis reveal ketonuria. Although results of the neurologic examination were normal at birth, by day 2 the infant is hypotonic, exhibits absent suck reflex, and has

decreased Moro and grasp reflexes with brisk deep tendon reflexes. No particular odor is noted on physical examination. At the time of interinstitutional transfer, she is noted to be encephalopathic. In view of persistent respiratory alkalosis, metabolic acidosis, hyperammonemia, and deteriorating neurologic status, the infant is transferred to our tertiary care NICU for further evaluation and management, including possible dialysis. Additional testing and recommendations from consultation services confirm the diagnosis.

*Take a moment to consider the diagnosis in this infant.*

## Diagnosis

Early laboratory findings of hypoglycemia, hyperammonemia, metabolic acidosis, and ketonuria and subsequent studies demonstrating neutropenia and thrombocytopenia with additional clinical signs of encephalopathy, hypothermia, and respiratory distress suggest the infant suffers from an inborn error of metabolism. The presence of hyperammonemia with concurrent metabolic acidosis indicates her diagnosis is most likely an organic acidosis, possibly propionic acidemia or methylmalonic aciduria. Isovaleric acidemia and maple syrup urine disease may present similarly but are associated with particular odors. Urine organic acid studies, as well as the results of New York Newborn State Screening tests, confirm she has propionic acidemia.

## Clinical Course

The infant begins an amino acid-free nutritional regimen with a 10% dextrose solution and intralipids at time of admission to our tertiary care NICU. Throughout her admission, her maximum ammonia levels were 806  $\mu\text{mol/L}$ , but she did not require dialysis. She transitioned to orogastric feeding consisting of a mixture of ammonia-free formula and a mixture of term formula/expressed human milk along with protein-free parenteral nutrition supplementation. The infant receives supplementation with carnitine, Ammonul® (Ucyclyd Pharma Inc, Scottsdale, AZ; sodium phenylacetate and sodium benzoate), and hydroxocobalamin. Ammonul and hydroxocobalamin are discontinued when ammonia levels normalize and the diagnosis is confirmed. She is neutropenic and thrombocytopenic during admission, requiring a platelet transfusion.

On day 6, the infant is unresponsive to stimuli and is extremely hypotonic with bilateral clonus, which suggests encephalopathy. An electroencephalogram shows electroclinical seizures in the left frontal region associated with right leg movement. Head ultrasound on the same day reveals left anterior periventricular white matter and thalamic echogenicity, likely secondary to ischemic changes. Pediatric neurologists are consulted and recommend treatment with phenobarbital.

The infant is discharged on day 24 after significant clinical improvement and normal ammonia levels. A protein-restricted diet consisting of a mixture of ammonia-free formula and expressed human milk or term formula is prescribed by the pediatric geneticists. PredischARGE head magnetic resonance imaging shows brain edema and mild cerebellar atrophy but no evidence of acute infarct. She is closely followed up by pediatric genetics, neurology, and ophthalmology subspecialties.

Since the infant's discharge from the NICU, she has been readmitted multiple times for poor feeding, emesis, and hyperammonemia as well as for a viral infection triggering respiratory failure. Currently, she is at home receiving a mixture of ammonia-free formula/soy-based formula, and her seizures are controlled with phenobarbital.

## Discussion

The incidence of all forms of inborn errors of metabolism is 1 in 800 to 1 in 2,500 births. Inheritance patterns vary, but the majority of these disorders occur via an autosomal recessive manner. Most disorders causing inborn errors of metabolism are due to a single defect in the processing of a particular protein, which disrupts the contiguity of a specific metabolic pathway. This action often leads to an accumulation of particular precursors and a deficit of other downstream metabolites, which may have important physiologic roles. Symptoms can be seen at any age. However, many forms present predominantly in infancy. Symptoms may include recurrent emesis, change in mental status (lethargy, irritability), seizures, changes in muscle tone, respiratory symptoms, and poor feeding. Specific physical examination findings can include atypical urine or body odor, rashes, alopecia, and organomegaly.

An initial evaluation includes assessment for infection with a complete blood cell count with differential, blood culture, and possibly examination of urine or cerebrospinal fluid cultures as well. Electrolytes, blood glucose, arterial blood gas, lactate, pyruvate, ammonia, plasma quantitative amino acids, and urine studies (reducing substances, organic acid, and urinalysis) should be sent if any suspicion of a metabolic disorder is present. If hyperammonemia is noted, the most likely diagnoses are urea cycle defects, organic acidemia, amino acid disorders, fatty acid oxidation defects, or transient hyperammonemia of the newborn. If metabolic acidosis is found in the setting of hyperammonemia, the differential narrows to only organic acidemia or fatty acid oxidation defects. Ketosis in this subset suggests the diagnosis is organic acidemia.

Organic acidemias occur in 3.7 per 100,000 to 12.6 per 100,000 births and are inherited as an autosomal recessive trait. The defect occurs in the catabolism pathway of amino acids, which leads to an accumulation of organic acids in the serum and urine. Propionic acidemia and methylmalonic aciduria are due to defects in the oxidation of the branched chain amino acids isoleucine, valine, threonine, methionine, odd-chain fatty acids, thymidine, uracil, and cholesterol. Specifically, propionic acidemia is caused by a deficiency of propionyl-coenzyme A (CoA) carboxylase resulting in the inability to break down propionyl-CoA into methylmalonyl-CoA, decreasing substrate for use in the citric acid cycle. Multiple gene mutations have been identified in patients who have propionic acidemia. The incidence is approximately 1 in 100,000 newborns.

Diagnosis of propionic acidemia is made by measuring urine organic acids with the use of gas chromatography–mass spectroscopy. The results will typically show increased propionic acid and methylcitrate, but methylmalonic acid will likely be decreased. The decreased methylmalonic acid helps differentiate this disorder from

methylmalonic aciduria. Standard New York State Newborn Screening tests can be used to diagnose this disorder as well. Prenatal diagnosis is possible by measuring enzyme activity in cultured amniotic fluid cells or chorionic villi cells.

Treatment involves maintenance on a low-protein diet (typically 8–12 g/day during infancy). The diet is typically supplemented with a formula preparation that does not contain amino acids, which are unable to be metabolized secondary to the deficiency of propionyl-CoA carboxylase. Ammonul is a metabolically active compound that serves as an alternative to urea for excretion of nitrogenous wastes, essential in the setting of hyperammonemia. Because there can be a relative carnitine deficiency in organic acidemias, supplemental carnitine provides a buffer to trap toxic acyl-CoA metabolites. Methylmalonic acidemia is occasionally due to reduced concentrations of its cofactor, cobalamin. In this setting, supplementation of hydroxocobalamin would augment the function of the methylmalonyl-CoA mutase enzyme.

Infants who are severely affected can die during the newborn period or later due to metabolic derangement, hypoglycemia, or infections. Cognitive development is adversely affected, and seizures are not uncommon. Magnetic resonance imaging changes in the basal ganglia region may occur. Pancreatitis and osteoporosis are noted at greater frequency in patients who have propionic acidemia.

### **Lessons for the Clinician**

Propionic acidemia and organic acid defects in general should be considered in a neonate who develops poor feeding, vomiting, hypoglycemia, irritability, lethargy, and hypotonia in the days after birth. Additional laboratory data of metabolic acidosis and hyperammonemia concomitantly should raise suspicions of organic acidemia even further. Early diagnosis allows for speedy intervention and decreases morbidity/mortality.

Meera Meerkov, MD, Maria del Mar Plata, MD, Alecia Thompson, MD, Jack D. Weiler Hospital of the Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY

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## **Lethargy, Stiffening, and Poor Feeding of Term Infant at 2½ Days of Age**

### **Presentation**

A 2½-day-old full-term infant born by induced vaginal delivery to a 33-year-old G1P1 mother with an uncomplicated pregnancy presents to the emergency department because of feeding refusal and severe apnea. She is found to have severe hypoglycemia and dehydration, but despite resuscitative efforts dies. Before presentation, at home the infant spit up yellow mucus-like material and had several episodes described as “lethargy” with stiffening of the legs. Appropriately vigorous at birth (Apgar scores of 9 at both 1 and 5 minutes), the infant received an initial feeding at the breast at 1 to 2 hours after birth. However, during the mother’s and infant’s hospital stay, subsequent feedings were erratic with markedly decreased interest in feeding and decreased vigor noted in the nursery. A sepsis evaluation in the nursery was negative. Tests including a second newborn screen and urine organic acids were sent to the lab, and the infant went home with results pending.

*Take a moment to consider the diagnosis in this infant.*

### **Discussion**

Qualitative organic acids showed elevated suberic, adipic, and sebacic acids consistent with dicarboxylic aciduria seen in disorders of fatty acid oxidation. Newborn screening obtained in the nursery showed elevated octanoyl carnitine (C8 acylcarnitine) of 26.37 micromolars (very elevated) consistent with medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD) in the infant. History revealed that the mother was of Mennonite ancestry, as well as no maternal or paternal episodes of metabolic decompensation or muscle weakness with stress or illness. DNA analysis for 2-point mutations in the medium-chain acyl-coenzyme A dehydrogenase (MCAD) gene revealed a heterozygous c.985A>G mutation. Additional testing on cord blood at a specialized clinic for gene sequencing of families without



the common MCAD point mutation c.985A>G was obtained. Mutational analysis identified 2 heterozygous point mutations in the MCAD gene including the common c.985A>G inherited from the father and a novel c.395C>G inherited from the mother, possibly associated with Mennonite ancestry.

### ***The Condition***

Medium-chain acyl-coenzyme A dehydrogenase is one of the enzymes involved in mitochondrial fatty acid  $\beta$ -oxidation, which fuels hepatic ketogenesis. It is a major source of energy once hepatic glycogen stores become depleted during prolonged periods of fasting or times of increased energy demand. Medium-chain acyl-coenzyme A dehydrogenase deficiency is an autosomal recessive disorder, which necessitates that both parents carry the mutation. The prevalence of the disease is approximately 1 in 5,000 to 1 in 15,000 whites, although the carrier frequency may be as high as 1 in 40 to 1 in 100. Children are usually normal at birth and typically present around 24 months of age. However, later presentations, including some in adulthood, have been reported. Furthermore, some patients with MCADD never develop any symptoms. Medium-chain acyl-coenzyme A dehydrogenase deficiency has an excellent prognosis once the diagnosis is appropriately established and frequent feedings are instituted to avoid periods of prolonged fasting. In a typical clinical scenario, a child with MCADD presents with hypoketotic hypoglycemia, vomiting, and lethargy triggered by a stress such as a common medical illness. Seizures due to hypoglycemia may occur, and symptoms may progress to coma and death. Hepatomegaly and acute liver disease are also often present. Medium-chain acyl-coenzyme A dehydrogenase deficiency is also associated with sudden infant death syndrome. Before diagnosis, MCADD may result in death or serious neurologic damage. However, these consequences have been significantly reduced secondary to expanded newborn screening.

Expression of MCADD is variable and depends on the type of mutation and the precipitating clinical events. The most common mutation associated with MCADD is the c.985A>G mutation. Subsequent risk of additional children with MCADD is 1 in 4. Based on newborn screening results, approximately 50% of affected individuals are homozygous for the common mutation, c.985A>G, and approximately 40% are heterozygous for c.985A>G and have 1 of more than 40 rare alleles.

### ***Diagnosis***

Clinically, the most common presentation of MCADD is fasting intolerance with episodes of hypoglycemic coma, hypoketotic dicarboxylic aciduria, low carnitine, fatty liver, encephalopathy, vomiting, and progressive deterioration that may prove

fatal. In the newborn period, frequent feedings typically mask symptoms due to little need for alternative fuel. However, when an infant has increased periods of time between feedings, the need for alternative fuel increases, and this correlates with preprandial irritability, lethargy, and possibly seizures secondary to severe hypoglycemia. Before such episodes of stress such as illness, patients often appear normal. Urine organic acids reveal a dicarboxylic aciduria. Plasma acylcarnitine profile and measurement of plasma carnitine confirm the diagnosis. Urinalysis is negative for ketones and blood may show hypoglycemia. Medium-chain acyl-coenzyme A dehydrogenase deficiency is often identified before clinical presentation on newborn screening, which will show elevated C8-carnitine values. DNA analysis most commonly shows at least one c.985A>G mutation, which accounts for 80% of MCADD alleles. In addition, about 52% of individuals with MCADD are homozygous for the common c.985A>G mutation.

### ***Differential Diagnosis***

The differential diagnosis of an infant who presents with lethargy, poor feeding, and periods of hypertonicity or hypotonicity includes asphyxia, sepsis, seizures, congenital heart defects, adrenal insufficiency, and inborn errors of metabolism (IEM) such as deficiencies in fatty acid oxidation, amino acid disorders, urea cycle defects, organic acidurias, congenital lactic acidosis, and mitochondrial disorders. It is important to recognize patients with IEM are often healthy at birth and present with nonspecific problems of lethargy, decreased feeding, and vomiting. Other early clinical signs of IEM include an abnormal odor to the urine or several types of hair and skin findings. The differential diagnosis for nonketotic or hypoketotic hypoglycemia includes hyperinsulinemia and fatty acid oxidation disorders.

### ***Treatment***

The management of patients with MCADD includes frequent feedings during the newborn period and infancy, as well as prompt attention to any intercurrent illness associated with catabolism. Glucose monitoring may also be instituted. In addition, many physicians supplement the diet with carnitine, as it permits the conjugation and excretion of toxic metabolites. Avoidance of prolonged periods of fasting, dehydration, and hypoglycemia is key, particularly in periods of illness or otherwise increased bodily stress.

## Lessons for the Clinician

Poor feeding and decreased vigor in an infant should be taken seriously, as this infant may have benefited greatly from prolonged observation and potential preparation for resuscitation in the nursery on the date of discharge.

When considering a diagnosis of an IEM, the physician should request an appropriate diagnostic evaluation such as plasma amino acids, urine organic acids, plasma acylcarnitine profile and carnitine concentrations, ammonia, and lactate.

Key elements in the patient's family history may also lead to a diagnosis in patients with IEM, including early loss of an infant or multiple miscarriages.

In MCADD, newborn screening and early recognition of the disease has led to significantly decreased morbidity and mortality.

Despite the time of decompensation in most cases of MCADD being outside the newborn period, there are occurrences of MCADD decompensation in neonates. Early decompensation may be associated with greatly elevated C8 concentrations (6  $\mu\text{mol/L}$  or greater).

Lastly, the novel pathogenic sequence variant (c.395C>G) has not been reported as a rare polymorphic variant. This demonstrates the importance of the conserved proline at amino acid 132. All species sequenced have proline at this position, highlighting the importance of this residue to enzyme function.

Jessica B. Duis, MD, Johns Hopkins Children's Center, Baltimore, MD; Jodie Martin, MS, Andrea Gropman, MD, Children's National Medical Center, Washington, DC; Erik Puffenberger, PhD, The Clinic for Special Children, Strasburg, PA

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## **Profuse Diarrhea in a 4-Day-Old Term Boy**

### **Presentation**

A term male infant with a birthweight of 3,015 g is born by normal spontaneous vaginal delivery to an immigrant mother from Ghana. The infant is admitted to the newborn unit; physical examination is significant for a natal tooth. The infant is fed mostly human milk with occasional formula feeds without any problem. On day 3, the infant develops hyperbilirubinemia and requires phototherapy. On the fourth day, the infant develops severe watery diarrhea, which is interpreted as phototherapy related. Diarrhea continues and serum chemistry shows hyperchloremic metabolic acidosis (arterial blood gas shows bicarbonate level of 7.9 mEq/dL; base excess (BE),  $-15$ ). The infant is transferred to the neonatal intensive care unit (NICU) for further evaluation. Clinically the infant is active and alert with a voracious appetite. He is taking 4 to 5 oz/feed, without clinical evidence of dehydration. Weight loss is only 155 g (about 5% of birthweight).

Family history reveals that a sibling had diarrhea as an infant, which resolved following cessation of breastfeeding.

The infant is admitted to the NICU on the fifth day and prescribed nothing by mouth (NPO), and diarrhea decreases soon after and then stops. The infant is restarted on human milk and diarrhea reappears. The infant is made NPO again and diarrhea stops again. The infant is tried on Alimentum/pregestamil, and the infant feeds well and is always hungry with no vomiting, but watery diarrhea becomes worse. After consultation with a pediatric gastroenterologist, the infant is made NPO for 1 day and starts on Neocate, which is tolerated well. The diarrhea stops, birthweight is regained, and he is discharged from the hospital to have follow-up with the pediatric gastroenterologist and his pediatrician. At present the infant is doing well and is gaining weight with normal growth and development.

Laboratory values showed hyperchloremic metabolic acidosis (sodium, 141 mmol/L; potassium, 4.6 mmol/L; chloride, 120 mmol/L; CO<sub>2</sub>, 14 mmol/L; RpT: sodium, 137 mmol/L; potassium, 3.8 mmol/L; chloride, 117 mmol/L; CO<sub>2</sub>, 9 mmol/L; anion gap, 12 mmol/L, normal [NL] range 7 to 14). The infant's electrolytes showed hyperchloremic, nonanionic gap metabolic acidosis during episodes of diarrhea, which stabilized once the infant was placed on nothing by mouth on IV fluids. Once the infant was started on Neocate, hyperchloremic metabolic acidosis resolved: arterial blood gas was pH, 7.31; PCO<sub>2</sub>, 16 mm Hg; PO<sub>2</sub>, 138 mm Hg; HCO<sub>3</sub><sup>-</sup>, 7.9 mmol/L; and BE, -15.4 mmol/L. Stool culture was negative, negative for occult blood, fat 2+, and positive for reducing substance. Blood culture was negative; pancreatic elastase, 242 (NL >200); vasoactive intestinal peptide, 24.4 (20 to 42 pg/mL); ammonia, 115 mmol/L; and complete blood cell count (white blood cells, 15.3 k; hemoglobin, 13.4 g/dL; platelets, 445,000; glucose-6-phosphate dehydrogenase, NL; and liver function tests, NL). Metabolic screen was negative for galactosemia and thyroid disorder. Urine testing for organic acids was negative.

*Take a moment to consider the diagnosis in this infant.*

## **Clinical Presentation**

Based on the clinical presentation and response to the treatment, this infant seems to have congenital glucose/galactose malabsorption (GGM). Infant had profuse diarrhea starting on the fourth day after birth despite switching the feedings (human milk/Alimentum/Pregestamil). Diarrhea stopped with discontinuance of the feeds and restarted soon after reintroduction of those feeds. Infant also developed hyperchloremic, nonanion gap metabolic acidosis. Clinically the infant was an active, alert, hungry infant with a good appetite and suck.

Infant responded well to Neocate with no diarrhea and normal growth and development.

## **Genetics of the Disease**

Glucose/galactose malabsorption is an autosomal recessive disorder caused by a mutation in Na<sup>+</sup>/glucose cotransporter (SGLT) gene *SLC5A1*. More than 40 mutations of *SLC5A1* responsible for GGM have been described.<sup>1</sup>

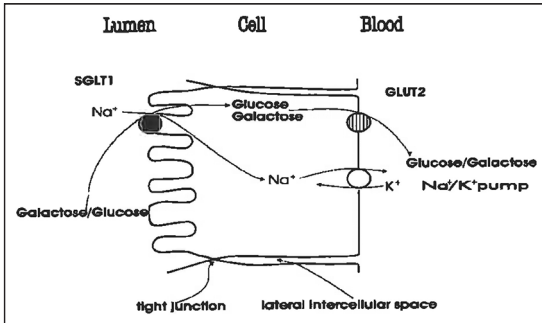
In a report in 1962 from Sweden, GGM has been recorded from several different parts of the world.<sup>2,3</sup> There is no ethnic predilection, but consanguinity plays a very important role as there are multiple case reports from Middle Eastern countries and the Amish population. It is more common in female infants.<sup>1</sup> More than 200 cases have been reported worldwide since its first report.<sup>1</sup>

## Pathophysiology of the Disease

Glucose is the main fuel providing energy for regular metabolic needs of humans. Glucose is transported across the plasma membrane by a carrier protein called “glucose transporter.” Glucose transporters (GLUTs) are divided into two families: 1) the facilitative diffusion GLUT and 2) SGLT. Both GLUTs and SGLTs belong to one of the 43 families of solute carrier genes (*SLC1–SLC43*).

Transepithelial glucose transport occurs by a coordinated action of SGLTs (in small intestine/renal tubules/salivary glands) allowing glucose influx through luminal membrane. Glucose transporters allow glucose efflux through the basolateral membrane.

Glucose/galactose is handled by SGLT1. Fructose is absorbed passively across brush border by fructose uniporter GLUT5 and by GLUT2 across basolateral membrane as shown in Figure 35.1.<sup>4</sup>



**Figure 35.1.** Illustration of the current model for glucose and galactose transport across the mature enterocytes of the small intestine. SGLT1 refers to the Na<sup>+</sup>/glucose cotransporter and GLUT2 refers to the facilitated glucose transporter (uniporter). Fructose is absorbed passively by a fructose uniporter in the brush-border membrane (GLUT5) and by GLUT2 in the basolateral membrane. With kind permission from Springer Science + Business Media: *Cell Biochemistry and Biophysics*, “Molecular basis for glucose-galactose malabsorption,” vol 36, 2002, Ernest M. Wright, Eric Turk, Martin G. Martin, Figure 1.

## Diagnostic Criteria for Glucose/Galactose Malabsorption

1. watery diarrhea soon after birth
  - a. clinical improvement on withdrawal of dietary glucose and galactose
  - b. relapse on reintroduction of glucose/galactose
  - c. biopsy—histologic normal small intestinal mucosa—normal mucosal disaccharidase activities
  - d. absorptive defect confined to glucose and galactose

2. Prenatal diagnosis in affected families
3. Intermittent or permanent glycosuria after fasting or after a glucose load
4. Finding of positive reducing substance in watery stool and slight glycosuria despite low blood sugar is highly suggestive
5. Interval breath hydrogen test

### **Differential Diagnosis**

Diarrheal diseases presenting in the neonatal period appear in Table 35.1 (used with permission, modified for this review).

**Table 35.1. Differential Diagnosis: Diarrheal Diseases Presenting in the Neonatal Period**

<p>Condition:</p> <ul style="list-style-type: none"> <li>• Congenital microvillus atrophy</li> <li>• Tufting enteropathy</li> <li>• Congenital glucose-galactose malabsorption</li> <li>• Congenital lactase deficiency</li> <li>• Congenital chloride diarrhea</li> <li>• Cong. defective Na/H exchange</li> <li>• Cong. bile acid malabsorption</li> <li>• Cong. enterokinase def.</li> <li>• Enteric anendocrinosis (NEUROG 3 mutation)</li> </ul> <p>Other causes:</p> <ul style="list-style-type: none"> <li>• Congenital sucrase isomaltase deficiency</li> <li>• Gastrinoma, VIPoma</li> <li>• Milk protein allergy</li> </ul>	<p>Clinical features:</p> <ul style="list-style-type: none"> <li>• Intractable watery diarrhea—Hypotonic dehydration</li> <li>• Intractable diarrhea—Partially respond to fasting</li> <li>• Intractable watery diarrhea—Hyperchloremic metabolic acidosis</li> <li>• Acidic diarrhea</li> <li>• Acidic diarrhea</li> <li>• Intractable watery diarrhea—Hypochloremia/Hyponatremia</li> <li>• Alkalosis</li> <li>• Intractable watery diarrhea—Hyponatremia/Metabolic acidosis</li> <li>• Steatorrhea</li> <li>• Failure to thrive, edema</li> <li>• Hyperchloremic acidosis—accompanying features, vomiting, diarrhea ceases with fasting, but returned with glucose/amino acids solution.</li> <li>• Infant asymptomatic when on diet containing Lactose (BF), in Eskimos</li> <li>• Neuroendocrine tumors: Older age group, tea colored odorless water stool—persists with fasting. Hypokalemia, hypochlorhydria usually presents later, GE reflux constipation</li> </ul>
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The contents of this table were published in *Nelson Textbook of Pediatrics*, 18th ed., Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. "Diarrheal Disease Presenting in the Newborn Period", p. 1589, Copyright Saunders Elsevier, 2007.

## Discussion

This case had the classic presentation of an active, alert infant with a voracious appetite who presented with severe watery explosive diarrhea and hyperchloremic acidosis. There was also a family history of a 9-year-old sibling with a similar clinical presentation. The infant responded well to Neocate with no diarrhea and normal growth and development. Human milk and Similac both have lactose as the sugar, which breaks into glucose and galactose.

On the other hand, Alimentum and Pregestamil are extensively hydrolyzed proteins (cow milk protein-based). Pregestamil contains corn syrup and modified corn-starch. Alimentum contains sucrose and modified tapioca starch, which are glucose polymers, which break down to d-glucose. In contrast Neocate is an amino acid-based formula (not cow milk protein) and has fructose as sugar base (carbohydrate as corn syrup, which is fructose). Fructose is absorbed passively by fructose uniporter in the brush border membrane (GLUT5) and by GLUT2 in the basolateral membrane.

The disease classically presents during the neonatal period or soon after the introduction of feedings of either human milk or formula, with life-threatening, profuse watery diarrhea and hypernatremic dehydration with metabolic acidosis.<sup>5</sup> Infants are usually very vigorous, nurse very well, and have a voracious appetite, regardless of their illness, and have irritability with abdominal distension and increased bowel sounds and failure to thrive. There is sudden cessation of diarrhea with fasting or the removal of offending sugar lactose (glucose/galactose), which is present in human milk and standard formula and glucose polymers present in Pregestamil and Alimentum, followed by normal growth and development. However, diarrhea reappears rapidly with reintroduction of a diet containing the offending sugar.

After going through the list of differential diagnoses (Table 35.1), family history of similar clinical presentation, and the clinical response to Neocate (fructose as carbohydrate), the diagnosis of GGM was made. Since the introduction of Neocate, the infant's growth and development have been normal.

Biopsy was not offered to the family to confirm the diagnosis because 1) there was a family history of similar illness; 2) there was a clinical presentation of watery diarrhea with hyperchloremic acidosis and an active, alert infant with voracious appetite; and 3) diarrhea resolved with removal of offending sugar. Had the infant not responded to our current management, we would have considered biopsy.

## Nutrition Management

Once a presumptive diagnosis is made based on the clinical features, nutritional management involves providing the infant with glucose/galactose-free formulas. As regular formulas contain lactose (source of glucose/galactose), specialized formulas



containing corn syrup as a sugar source, such as Neocate or Ross Carbohydrate Free Formula or Mead Johnson Product 3232A monosaccharide- and disaccharide-free powder, need to be used. Fructose is added to meet the energy requirement. Detailed dietary guidelines are available.<sup>6</sup>

### **Long-Term Prognosis**

Tolerance to carbohydrate-containing drinks improves gradually. Most of the patients are able to tolerate regular carbohydrate-containing diets, although the degree of improvement varies. The mechanism remains unclear.

Nephrocalcinosis and proximal tubular dysfunction have been reported as complications.

### **Lessons for the Clinician**

Diarrhea in the newborn is a very uncommon disorder, but it could be fatal if there is a delay in the diagnosis. A high index of suspicion and a few simple tests will help the clinician treat such infants without doing complicated investigations.

Resmy P. Gopi, MD, S. Khanna, MD, B. K. Rajgowda, MD, Department of Pediatrics/Division of Neonatology, Lincoln Medical and Mental Health Center, Bronx, NY

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### **COMMENT BY JOSEF NEU, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE**

This entity may be difficult to discern at first presentation from microvillus inclusion disease, but the latter usually does not respond to dietary therapy and has a poor prognosis.

*Part 9*

# **Maternal-Fetal Medicine**

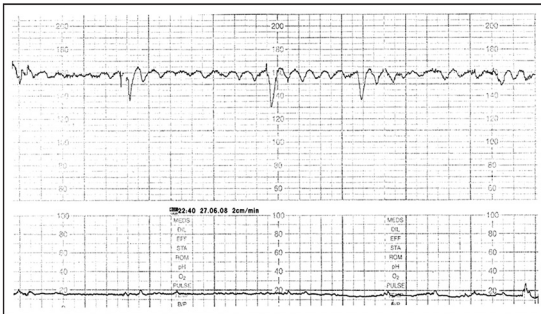
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# Diagnostic Fetal Heart Tracing

## Presentation

A newborn boy is admitted to the neonatal intensive care unit (NICU) because of pallor and respiratory distress. His mother is a 32-year-old primigravida, who has type 2 diabetes mellitus and whose prepregnancy treatment with metformin was changed to insulin early in the pregnancy. In the first trimester, the mother had a throat infection that was treated with clarithromycin. Results of routine antenatal serologic screening, ultrasonography, and fetal echocardiography were normal.

The mother presented to the hospital with decreased fetal movements at 36 weeks and 3 days of gestation. Electronic fetal heart rate monitoring (EFM) was performed (Figure 36.1) and she returned home. Several hours later, after review of the EFM record, she was recalled but could not be reached until the next morning, when EFM was repeated (Figure 36.2).



**Figure 36.1.** Initial electronic fetal heart rate monitoring strip.



**Figure 36.2.** Second electronic fetal heart monitoring strip.

A pale and nonvigorous male baby, who had a heart rate of 80 beats/min, was delivered by urgent cesarean section. He was resuscitated with bag-and-mask ventilation for 60 seconds followed by 100% free-flow oxygen; oxygen saturation was 75% at 3 minutes. His birthweight was 2.6 kg, his Apgar scores were 5 at 1 minute and 6 at 5 minutes, and his umbilical venous pH was 7.20.

On admission to the NICU, the infant's physical examination shows extreme pallor, tachypnea, mild-to-moderate subcostal retractions, nasal flaring, and intermittent grunting. His oxygen saturation is 92% on nasal continuous positive airway pressure of 5 cm H<sub>2</sub>O and FiO<sub>2</sub> of 0.35. Pulmonary and cardiac auscultation yield normal results. His pulse is weak, and capillary refill time is 4 seconds. His heart rate is 200 beats/min, and oscillometric blood pressure cannot be obtained. His liver and spleen are not palpably enlarged. Neurologically, he is alert but irritable, he has normal muscle tone, he moves all limbs normally, and anterior fontanelle tension is normal. Laboratory investigations reveal the diagnosis.

## Discussion

The infant's hemoglobin was 2.9 g/dL (29 g/L). Group O, Rh-negative packed red blood cells (PRBCs) were requested, and 2 intravenous boluses of normal saline, each 10 mL/kg over 15 minutes, were administered while awaiting PRBCs. Umbilical venous and arterial catheters were inserted. The mean arterial pressure ranged from 44 to 53 mm Hg. Following a transfusion of group O, Rh-negative PRBCs (20 mL/kg over 30 minutes), the hemoglobin increased to 7.7 g/dL (77 g/L). A further transfusion of 20 mL/kg cross-matched PRBCs was administered over 2 hours. Following these therapies, the hemoglobin was 12.7 g/dL (127 g/L), the heart rate was 150 beats/min, and perfusion had improved.

The initial arterial blood gas results were pH of 7.09, PO<sub>2</sub> of 45 mm Hg, and base deficit 16.3 mEq/L. Arterial lactate was 88.8 mg/dL (9.86 mmol/L). There was no evidence of renal or hepatic injury that might have resulted from hypovolemic shock.

*Take a moment to consider the diagnosis in this infant.*

A Kleihauer-Betke test on maternal blood was strongly positive for fetal red cells, indicating a fetomaternal hemorrhage (FMH) of approximately 200 to 230 mL. Magnetic resonance imaging of the infant's brain at 72 hours was read as normal. The infant's discharge examination on day 7 yielded normal results. On follow-up at 9 months of age, the infant was doing well and had reached the appropriate milestones for his age.

The clinical presentation was of anemia and hypovolemic shock. The sinusoidal electronic fetal heart rate pattern 12 hours prior to delivery was highly suggestive of fetal anemia. The causes of anemia in a newborn include a broad number of conditions (Table 36.1), but the positive Kleihauer-Betke test confirmed the diagnosis of FMH as the cause of anemia in this patient.

**Table 36.1. Causes of Anemia in Newborns**

Hemorrhagic Anemia	
• Fetal hemorrhage	• Umbilical cord bleeding
Spontaneous fetomaternal hemorrhage	Rupture of umbilical cord with precipitous delivery
Hemorrhage following amniocentesis	Rupture of short or entangled cord
Twin-twin transfusion	• Postpartum hemorrhage
Nuchal cord	Bleeding from the umbilicus
• Placental hemorrhage	Cephalhematomas, scalp hemorrhages
Placenta previa	Hepatic rupture, splenic rupture
Abruptio placentae	Retroperitoneal hemorrhages
Multilobed placenta (vasa previa)	
Velamentous insertion of cord	
Placental incision during cesarean section	
Hemolytic Anemia	
• Immune disorders	
Isoimmune: Rh and ABO incompatibility	
Maternal immune disease: autoimmune hemolytic anemia, systemic lupus erythematosus	
Drug-induced: penicillin	
• Acquired red blood cell disorders	
Infection: cytomegalovirus, toxoplasmosis, syphilis, bacterial sepsis	
Disseminated and localized intravascular coagulation, respiratory distress syndrome	
• Hereditary red blood cell disorders	
Membrane defects: hereditary spherocytosis, hereditary elliptocytosis	
Enzyme abnormalities: glucose-6-phosphate dehydrogenase, pyruvate kinase	
Hemoglobinopathies: alpha-thalassemia syndromes, gamma/beta-thalassemia	
Aplastic Anemia	
• Blackfan-Diamond anemia	

Data from Mentzer W, Glader B. Erythrocyte disorders of infancy. In: Taeusch W, Ballard R, Gleason C, eds. *Avery's Diseases of the Newborn*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2005:1180.

## The Condition

Fetomaternal hemorrhage is defined as the passage of fetal red blood cells (RBCs) into the maternal circulation. Such passage occurs in 40% to 50% of all pregnancies but in minute amounts.<sup>1</sup> The exact pathophysiology is unknown. Massive FMH of more than 80 mL may occur in 1 in 1,146 pregnancies and transfusions of more than 150 mL in 1 in 2,813 pregnancies.<sup>2</sup> Fetomaternal hemorrhage can occur at any time in pregnancy but most often during the third trimester and during labor.<sup>3</sup> Most cases are of unknown cause, although cases have been associated with abruptio placentae, vasa previa, chorioangioma, choriocarcinoma, thrombus of the umbilical vein, trauma, amniocentesis, and external cephalic version.<sup>4</sup>

Fetomaternal hemorrhage can occur acutely or chronically throughout the pregnancy. The degree and acuity of the hemorrhage determines the clinical presentation of the fetus or newborn and affects the prognosis. In the chronic form, which involves slower blood loss, the infant can present with severe anemia but have minimal symptoms or be asymptomatic. In acute cases, the infant may exhibit hydrops or be stillborn. The mother often presents with a history of decreased or absent fetal movements. Electronic fetal heart rate monitoring shows signs of fetal distress, as in decreased heart rate variability, late decelerations, bradycardia, and sinusoidal heart rate pattern. The sinusoidal fetal heart rate, first described by Modanlou and Freeman in 1982, is believed to be pathognomonic of fetal anemia. The newborn can present with signs of anemia (pallor and tachycardia), hypovolemic shock, or even asphyxia.<sup>1,3,4</sup>

There are no large follow-up studies of infants who suffered from FMH, and the small studies have only had follow-up until the age of 1 year. However, case reports confirm that, in cases of a massive FMH, the child can develop a stroke or periventricular leukomalacia, which can lead to cerebral palsy.<sup>4</sup>

If FMH is diagnosed before birth, management depends on the gestational age. After 34 weeks of gestation, delivery is recommended if signs of fetal anemia or acute fetal distress are present. Before 34 weeks of gestation, the options vary according to the severity of the FMH. In mild cases, very careful serial monitoring or in utero transfusion are possible; intrauterine transfusion or the delivery of the fetus may be indicated in severe cases.<sup>3,5</sup>

The Kleihauer-Betke test is the recommended test to detect FMH in cases of unexplained fetal distress, fetal death, or neonatal anemia. The test uses acid elution of maternal cells and the subsequent staining of fetal cells. Maternal erythrocytes are ruptured and appear as ghost cells, whereas the fetal RBCs stain strongly because of the stability of the fetal hemoglobin in an acid medium.<sup>6</sup> The fetal RBCs are counted as a proportion of the adult RBCs, and a quantitative estimate of the blood transfused from fetus to mother is determined using a formula.<sup>7</sup> One fetal RBC per 1,000 adult RBCs corresponds to a transfusion of about 5 mL of fetal blood into the mother's circulation.<sup>3</sup>

The test lacks some accuracy because maternal fetal hemoglobin increases during pregnancy. Also, it can present false-positive results in mothers who have hematologic conditions that increase hemoglobin F concentrations (thalassemia, sickle cell anemia). It can present false-negative results in situations where there is ABO incompatibility and where the fetus has received intrauterine transfusion.<sup>4</sup>



Some other tests can detect FMH, including the rosette test, the micro deoxyuridine test, gel agglutination, and flow cytometry. However, these tests are only useful when the mother is Rh-negative and the fetus is Rh-positive because they depend on detection of RhD-positive RBCs. Only the flow cytometry test gives a quantitative result. Alpha-fetoprotein measurement in the mother has been shown to correlate with FMH. However, this test can yield false-positive results in many fetal conditions. Fluorescence in situ hybridization and DNA amplification currently is used as a research tool but is promising as an extremely sensitive tool.<sup>6</sup>

### **Lessons for the Clinician**

In the presence of a history of decreased fetal movements accompanied by EFM showing a sinusoidal fetal heart rate, the clinician should prepare for resuscitation of an anemic infant and order group O Rh-negative blood for the delivery. A Kleihauer-Betke test should be ordered for the mother in any case of fetal death, anemia, or distress of unknown cause. Volume resuscitation with PRBCs should be performed promptly in an infant who has hypovolemic shock due to acute blood loss. Finally, it is important to diagnose FMH because it can have important repercussions on the infant's future neurodevelopment.

Ahmed Moussa, MD, John Smyth, MD, Women's and Children's Health Centre of British Columbia, Division of Neonatology, University of British Columbia, Vancouver, British Columbia, Canada

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## No Visible Fetal Stomach Bubble and Elevated Amniotic Fluid Index

### The Case

#### *Polyhydramnios*



**Figure 37.1.** Fetal ultrasonography at 34 weeks' gestation showing polyhydramnios.

#### *Maternal History*

A 17-year-old G1P0 mother. Prenatal laboratory values were normal.

The pregnancy was complicated by significant polyhydramnios.

At an estimated gestational age (EGA) of 29 weeks, fetal ultrasonography demonstrated no fetal abnormalities, but the stomach was not visible, and the amniotic fluid index (AFI) was elevated at 45 cm (normal, <24 cm). Amniocentesis performed at that time removed 1,400 mL fluid, karyotype was normal, and the AFI after the procedure was 28 cm.

Repeat fetal ultrasonography performed at 30 weeks' EGA revealed an AFI of 43 cm, and the stomach bubble still was not visible. Amnioreduction removed 1,150 mL of fluid; the postprocedure AFI was 35 cm.

Fetal ultrasonography performed at 33 weeks' EGA documented an AFI of 43 cm. (Figure 37.1). Amnioreduction was performed, and 3,000 mL of fluid was removed, resulting in a postprocedure AFI of 20 cm.

Three days later, at an EGA of 34 weeks, labor ensued.

### **Case Progression**

Spontaneous rupture of membranes occurred the following morning, and cervical dilation was 3 cm.

### **Differential Diagnosis**

#### ***Polyhydramnios With No Stomach Bubble***

##### *Digestive tract anomalies*

Nasopharyngeal tumors (teratoma, goiter, epulis, epignathus)

Cleft lip and/or cleft palate

Hypopharyngeal and laryngeal stenosis, webs, and clefts

Craniofacial syndromes (Pierre-Robin, Crouzon, Treacher Collins, Goldenhar, agnathia-holoprosencephaly, agnathia-microstomia-melotia)

Tracheoesophageal fistula and esophageal atresia

##### *Neuromuscular Defects*

Central nervous system disease (anencephaly, acrania, hydranencephaly, microcephaly)

Peripheral nervous system disease

Neuromuscular disease (myotonic muscular dystrophy, Pena-Shokeir syndrome)

**Take a moment to consider the diagnosis in this infant.**

## Actual Diagnosis

### *Mandibular Hypoplasia/Agnathia-Otocephaly*

Surgical consultation was obtained, and an ex utero intrapartum treatment (EXIT) procedure was planned. This procedure is used commonly when difficulties are anticipated in obtaining access to and maintaining the patency of the infant's airway (eg, severe micrognathia, large neck masses). A cesarean section is performed under deep general anesthesia (to enhance uterine relaxation and to provide anesthesia for the infant). The head and neck are delivered while the placenta continues to perfuse the infant. Intubation is attempted; if unsuccessful, a tracheostomy is performed while the fetus is on the mother's abdomen. Once the airway is secured, the umbilical cord is cut, and the infant is taken to the radiant warmer, where resuscitation is provided as needed.<sup>1</sup>

In this case, a designated resuscitation team was present in the delivery room, as were specialists from pediatric surgery and pediatric anesthesia. The head and upper chest of the infant were delivered, but intubation was not attempted because of the severity of the mandibular hypoplasia (Figure 37.2).



**Figure 37.2.** Infant born at 34 weeks' gestation with severe mandibular hypoplasia.

Tracheostomy was performed immediately by the pediatric surgeon. Positive pressure ventilation was provided through the tracheostomy tube, the delivery was completed, and the umbilical cord was cut.

The infant was taken to the radiant warmer, where he demonstrated no respiratory effort. His initial heart rate was greater than 100 beat/min. Despite manipulation of the tracheostomy tube position, the resuscitation team was unable to obtain visible chest rise with increasing positive pressure ventilation. Resuscitative efforts were discontinued after 50 minutes (Figure 37.3).

Umbilical cord gas (arterial) measurements at delivery demonstrated

- pH, 7.28
- $\text{PCO}_2$ , 52 mm Hg
- $\text{PO}_2$ , 26 mm Hg
- $\text{HCO}_3$ , 23 mmol/L
- Base excess, -5 mEq/L

Arterial blood gas measurements from the delivery room demonstrated

- pH, 6.67
- $\text{PCO}_2$ , 185 mm Hg
- $\text{PO}_2$ , 2 mm Hg
- $\text{HCO}_3$ , 21 mmol/L
- Base excess, -29.2 mEq/L

Autopsy demonstrated agnathia, microstomia, and hypoglossia. However, there was no anatomic explanation for the inability to ventilate the infant. Possibly there was airway obstruction, perhaps minor malformation of the trachea that would prevent tracheostomy ventilation.



**Figure 37.3.** Newborn with severe mandibular hypoplasia who required an emergent tracheostomy but was unable to be ventilated effectively and died at 50 minutes of age.

## The Experts

### *Embryology*

The head and neck are formed via the pharyngeal apparatus, which consists of arches, pouches, grooves, and membranes. The first branchial arch is involved in formation of the face. Pharyngeal or branchial arches form as neural crest cells migrate from the hindbrain during the fourth and fifth weeks of gestation. The first arch develops into the maxillary and mandibular prominences. From the mandibular swelling comes Meckel's cartilage, the dorsal end of which ossifies to become the malleus and incus. The intermediate portion of the cartilage regresses. The ventral portion of Meckel's cartilage disappears, and the mandible develops around it by intramembraneous ossification. The tongue is formed from the first and third pharyngeal arches. The larynx develops as a laryngotracheal diverticulum in the fourth week of intrauterine life. The face develops as five facial primordial processes around the primitive mouth. The mandibular processes merge in the fourth week of gestation, giving rise to the lower jaw, lower lip, and lower aspect of the face. Ears develop in the fifth week from swellings around the first pharyngeal groove. Initially they are located in the neck area, but as the mandible develops, they ascend.<sup>2</sup>

### *Otocephaly*

Errors in craniofacial development result in a spectrum of anomalies, ranging from isolated cleft palate to enormous facial clefts. Otocephaly is a rare, lethal malformation comprising hypoplasia or absence of the mandible (agnathia), ventromedial displacement and often fusion of the auricles (synotia or otocephaly), and hypoplasia of the oral cavity (microstomia) and tongue (hypoglossia). It is believed to result from arrested development of the first branchial arch, perhaps due to a neural crest cell insult.<sup>3</sup> The anatomic subclassification of agnathia-otocephaly complex includes agnathia-otocephaly, agnathia-otocephaly with holoprosencephaly, agnathia-otocephaly with situs viscerum inversus, and agnathia-otocephaly with holoprosencephaly and situs inversus.

Approximately 80 cases have been published since 1717 (Kerckring),<sup>1</sup> and the estimated prevalence is 1 in 70,000. Neither chromosomal anomalies nor teratogenic factors have been clearly identified; agnathia-otocephaly complex appears to be a sporadic event. Based on studies in sheep, some have attributed the event to maternal salicylate or theophylline use. It has been speculated to be caused by a failure of neural crest cells to migrate in the first pharyngeal arch, but it is unclear whether the problem is with migration, proliferation, or differentiation.

All comparable cases present with the following variations: the mandible is rudimentary or absent; the middle ear ossicles and bones of the facial skeleton are malformed or reduced in size; and soft-tissue variations include an absence of salivary

glands and anomalous positioning of the tongue and deficiencies in its musculature. Absence or marked underdevelopment of the mandible is the major defect and can explain the failure of related cartilaginous structures to develop or to be positioned normally.

Milder forms of this syndrome include Treacher-Collins (autosomal dominant, malar hypoplasia, lower eyelid defects, and malformed ears) and Pierre-Robin (mandibular hypoplasia results in posterior displacement of the tongue and subsequent impairment of fusion of the palate).

Only one survivor who had complete mandibular agenesis has been reported in the literature (1985).<sup>2</sup> At the time of the report, the child was 3 years old and had a tracheostomy and gastric tube, but no reconstructive efforts had been attempted. Hearing and sight were intact, and he communicated via sign language. Reconstructive surgeons opted for reconstruction of the mandible with tissue from his ribs to improve appearance; they were not hopeful that he would speak or chew.

Becky Ennis, MD, JoDee M. Anderson, MD, University of Texas, Southwestern Medical Center at Dallas, Dallas, TX

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*Part 10*

# **Nephrology**



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# **Respiratory Distress, Flaccid Abdominal Musculature, and Cryptorchidism**

## **The Case**

A newborn male born at 35 weeks' gestation displays respiratory distress, flaccid abdominal musculature, and undescended testes.

### ***Prenatal History***

A 29-year-old G3 P10112 woman who has a healthy 8-year-old son.

Rubella-nonimmune, group B Streptococcus-positive.

Social history negative for medications, alcohol, tobacco.

Family history negative for renal or genitourinary anomalies.

Antenatal diagnosis of bladder outlet obstruction with posterior urethral valves, left cystic kidney, possible right talipes equinovarus, and oligohydramnios.

Amniocentesis revealed normal 46XY karyotype.

Placement of a fetal vesicoamniotic shunt at 23 weeks' gestation.

Repeat ultrasonography performed at 31 weeks' gestation revealed a decompressed bladder, left kidney with mild dilation and multiple small cysts, irregular abdominal musculature, and normal amniotic fluid volume.

Repeat ultrasonography at 33 weeks' gestation showed decreased amniotic fluid volume, prompting hospitalization of the mother for IV fluid hydration and corticosteroid administration.

***Birth History and Presentation***

Due to concerns for recurrent, self-resolved fetal heart rate decelerations, the infant was delivered via cesarean section at 35 weeks' gestation.

Apgar scores were 6 and 8 at 1 and 5 minutes, respectively.

Infant developed increased work of breathing in the delivery room and was intubated.

Birthweight: 2,590 g (50th percentile).

Length: 47.5 cm (50th to 90th percentile).

Occipitofrontal circumference: 27 cm (<3rd percentile).

***Case Progression******Vital Signs***

Temperature: 36.8°C

Heart rate: 152 beats/min

Respiratory rate: 40 breaths/min

Blood pressure: 68/37 mm Hg

***Physical Examination***

Intubated, pink, and well perfused

Relatively small chest, with subcostal retractions, fair aeration bilaterally

Regular heart rate and rhythm without murmur, normal pulses

Bulging abdomen, poor abdominal musculature that is flaccid to palpation and non-tender, palpable loops of bowel

Palpable left flank mass

Vesicoamniotic tube to the right of umbilicus draining urine

Normal penis with bilateral undescended testes

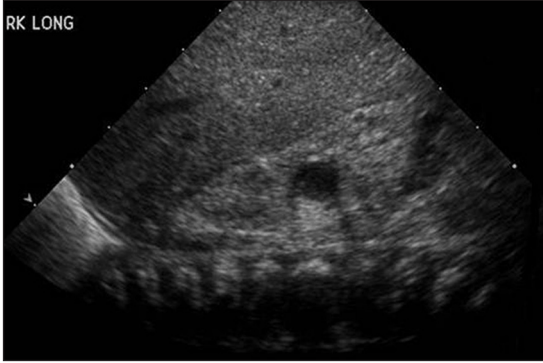
Right talipes equinovarus



**Figure 38.1.** Intubated infant at 35 weeks' gestation with distended abdomen and flaccid abdominal musculature.

### ***Radiologic Findings***

Bilateral cystic dysplastic kidneys with echogenic cortex and multiple small cortical cysts, bilateral dilation of the renal pelvis and ureters, decompressed urinary bladder



**Figure 38.2.** Renal ultrasonography showing multiple small cortical cysts.

### ***Differential Diagnosis***

#### ***Respiratory Distress, Flaccid Abdominal Musculature, and Cryptorchidism***

Megacystis megaureter

Megacystis-microcolon-intestinal hypoperistalsis syndrome

Neurogenic bladder

Posterior urethral valves

Prune belly syndrome

Severe primary vesicoureteral reflux

Ureteropelvic junction obstruction

Urethral obstruction

*Take a moment to consider the diagnosis in this infant.*

## Actual Diagnosis

### *Prune Belly Syndrome*

## The Experts

Prune belly syndrome (PBS), also known as Eagle-Barrett syndrome, is a rare condition characterized by the triad of absent or incomplete abdominal musculature, undescended testes, and urinary tract abnormalities. The incidence is estimated at approximately 3.8 cases per 100,000 live births, with a marked male predominance.<sup>1</sup> Recent epidemiologic data obtained from the Kids' Inpatient Database found 50% of PBS patients were white, 31% black, and 10% Hispanic.<sup>1</sup> Affected patients are often born preterm (43% of infants), and prematurity is associated with higher inpatient mortality.<sup>1</sup>

Although the exact inheritance pattern is unknown, PBS is most likely transmitted in a sex-influenced, autosomal recessive pattern, with some familial cases reported.<sup>2</sup> Of note, affected females are seen more commonly in the familial (28%) than the nonfamilial (5%) forms of PBS.<sup>2</sup> Prune belly syndrome has been observed in association with trisomy 13, 18, and 21.<sup>3,4,5</sup> In addition, one affected infant had a large deletion of the long arm of chromosome 6.<sup>6</sup>

The two primary theories regarding the pathogenesis of PBS are aberrant mesodermal development<sup>7,8</sup> and early urethral obstruction.<sup>9,10</sup> The mesodermal defect theory proposes that the constellation of anomalies is due to a defect in the intermediate and lateral plate mesoderm, which affects the development of the mesonephric and paramesonephric ducts as well as the abdominal musculature and urinary tract.<sup>8</sup> The urethral obstruction theory proposes that distal obstruction in early gestation results in distension of the bladder and ureters, urinary ascites, and degeneration of the abdominal muscles.<sup>11,12</sup>

Patients who have PBS can present with a variety of renal and urologic complications, including cystic renal disease, renal dysplasia, renal insufficiency, hypospadias, micropenis, urachal anomalies, and ureterocele.<sup>1</sup> Anomalies of the urinary tract can lead to impaired voiding, vesicoureteral reflux, repeat urinary tract infections, pyelonephritis, and renal scarring during childhood.<sup>13</sup> Among the extrarenal manifestations are pulmonary hypoplasia due to oligohydramnios and skeletal deformities (45%) such as talipes equinovarus, hip dysplasia, kyphoscoliosis, torticollis, and pectus excavatum.<sup>13</sup> In addition to pulmonary hypoplasia, many patients who have PBS develop chronic respiratory dysfunction due to associated skeletal anomalies and abdominal weakness; they are prone to recurrent respiratory infections and are at increased risk of respiratory complications after exposure to general anesthesia.<sup>14</sup> Cardiac abnormalities are seen in 10% of patients and include ventricular septal defects, tetralogy of Fallot, patent ductus arteriosus, and atrial septal defects.<sup>13</sup>

Gastrointestinal complications are seen in up to 30% of patients and include malrotation, intestinal atresias (often colonic) or stenoses, volvulus, and chronic constipation.<sup>12,15,16</sup> Although central nervous system anomalies are rare (5%),<sup>1</sup> many patients exhibit developmental delay and growth retardation as children.<sup>17</sup>

Prune belly syndrome is often diagnosed by prenatal ultrasonography as early as 13 weeks' gestation or upon physical examination at birth.<sup>18,19</sup> The severity of PBS is classified as grade 1: oligohydramnios, lung hypoplasia, and Potter facies; grade 2: moderate-to-severe involvement of the fetal urinary system without lung hypoplasia and without Potter facies; and grade 3: mild renal impairment.<sup>19</sup> The prognosis varies primarily according to the severity of renal impairment. Approximately 30% of patients who survive the neonatal period develop chronic renal insufficiency necessitating dialysis or transplantation during childhood or adolescence.<sup>13,20,21</sup> The overall mortality is estimated at 36% to 60%,<sup>1,22</sup> with most deaths occurring during the initial hospitalization or neonatal period.

Promising treatments include in utero placement of a vesicoamniotic shunt, which has been successful in restoring amniotic fluid volume and reducing neonatal mortality, although long-term outcomes in terms of chronic renal insufficiency are not yet available.<sup>23</sup> Postnatal treatment includes orchiopexy, abdominoplasty, renal transplant, and relief of bladder outlet obstruction (vesicostomy early and later Mitrofanoff).<sup>24</sup>

In conclusion, PBS is a rare disease primarily affecting males that is characterized by a triad of congenital anomalies (deficient abdominal musculature, cryptorchidism, and urinary tract abnormalities) and related complications. Early diagnosis and treatment can lead to improved perinatal outcomes, although long-term data regarding chronic renal disease are not yet available.

Morgan B. Wolfe Jr., Anne M. Beck, MD, Jennifer Wambach, MD, Washington University School of Medicine, St Louis, MO

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*Part 11*

# **Neurology**

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# Hypotonia and Arthrogryposis in a Neonate

## Presentation

A term male infant is admitted to the neonatal intensive care unit (NICU) after difficulty feeding and respiratory distress at 5 hours of age. The baby was born to a 35-year-old gravida 3 para 2 woman. All maternal laboratory results were negative during prenatal screening, although prenatal ultrasonography during the third trimester showed oligohydramnios and intrauterine growth restriction. The initial evaluation after delivery revealed an asymmetric, small-for-gestational age infant whose birthweight was 2,215 g and Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. On physical examination, the infant exhibited generalized hypotonia, poor suck with excessive oral secretions, symmetric Moro reflex and posture, normal reflexes, and arthrogryposis of the wrists and elbows. No tongue fasciculations were noted. The remainder of the physical examination showed normal results.

In the NICU, the infant is placed on bilevel positive airway pressure due to respiratory distress and antibiotics. Initial attempts to feed the baby orally fail due to persistent desaturations and bradycardia during feedings. Results of *Toxoplasma*, rubella, cytomegalovirus, and herpes simplex virus antibody assessment; lumbar puncture; blood and peripheral cultures; and antiacetylcholine receptor antibody assessment are negative. Additional laboratory work documents elevated creatine kinase (CK) of 9,472 units/L, lactate dehydrogenase of 891 units/L, aldolase of 27 units/L, aspartate aminotransferase of 98 units/L, and alanine aminotransferase of 137 units/L. Head computed tomography scan and magnetic resonance imaging yield normal results. By 1 month of age, the infant is weaned to room air, tolerates oral feedings, and is discharged from the hospital with close outpatient monitoring.

He continues to have poor tone and feeding difficulties and is admitted to the hospital at 2 and 3 months of age due to respiratory distress. At about 4 months of age, he is readmitted due to poor feeding and worsening hypotonia. His weight remains

below the third percentile, he has poor swallowing, and he takes 45 minutes to consume 4 oz of formula. His motor milestones are delayed, but all other milestones are appropriate for age. A test is performed that reveals the diagnosis.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

A muscle biopsy confirmed the diagnosis of congenital muscular dystrophy (CMD), with deficiency of laminin alpha-2 on histochemical staining. There was no family history of any neuromuscular disease. The mother reported that her two other children had a different father and had no medical problems.

### The Condition

Congenital muscular dystrophies are a set of genetically determined conditions in which muscular dystrophy is evident at birth. These dystrophies have been associated with mutations of various genes, including *LAMA2*, *FKRP*, *LARGE*, *COL6A1*, *COL6A2*, *COL6A3*, *SEPN1*, *FCMD*, *POMGNT1*, *POMT1*, *POMT2*, *ITGA7*, and *LMNA*. The serum CK concentration usually is elevated, and muscle biopsy characteristically is abnormal, with extensive fibrosis, degeneration and regeneration of muscle fibers, and proliferation of fatty and connective tissue.

Congenital muscular dystrophy is classified further on the basis of involvement of structural central nervous system (CNS) abnormalities detected by neuroimaging. The absence of structural changes distinguishes “classic” CMD from “syndromic” forms of CMD, such as Fukuyama muscular dystrophy, Walker-Warburg syndrome, or muscle-eye-brain disease. However, a few cases of classic CMD with structural lesions have been reported.

Classic forms of CMD are identified by mutations within the laminin alpha-2 chain gene. They are subclassified further into merosin-negative and merosin-positive groups. The mode of inheritance is autosomal recessive, and various gene loci, such as 6q22–q23, 1q42, 19q13.3, and 1p35–p36, have been reported to be involved.

Ullrich CMD and Bethlem myopathy are associated with extensive mutations in type VI collagen genes (*COL6A1*, *COL6A2*, and *COL6A3*). Although these conditions previously were believed to be separate entities, they now are considered opposite ends of a phenotypic spectrum. The mode of transmission is autosomal recessive, and there have been associations with genetic mutations on loci 21q22.3 and 2q37.

Fukuyama type, muscle-eye-brain disease, and Walker-Warburg syndrome are the types of CMD that typically are associated with CNS abnormalities and are autosomal recessive disorders. The various gene loci involved with these disorders are

9p31–q33, 1p32–p34, 19q13.3, 9q34.1, and 9q31–33. Brain magnetic resonance imaging shows hypodense white matter, hypoplastic cerebellum and pons, ventricular dilatation (with or without hydrocephalus), and abnormal cortical development known as cobblestone type brain malformation (also called type II lissencephaly). Other malformations include Dandy-Walker cyst, sometimes associated with posterior encephaloceles.

## Diagnosis

The infant who has any type of CMD typically presents in the newborn period as a “floppy” baby, often with arthrogryposis. Magnetic resonance imaging of the brain is useful to look for structural lesions or white matter abnormalities that accompany some CMDs. Examination of the eyes is important to exclude an ocular abnormality. Infants who have CMDs have variably elevated serum CK values.

Molecular genetic testing allows for confirmation of some forms of CMD, including those associated with mutations in *LAMA2*, *FKRP*, *POMT1*, *POMT2*, *fukutin*, *POMGnT1*, and *LARGE1*. The diagnosis also can be confirmed by muscle biopsy findings of widespread dystrophic changes or a myopathic pattern. For infants lacking merosin, muscle immunohistochemical examination with antimerosin antibodies usually reveals an absence of this protein in the sarcolemma of the muscle fibers.

## Differential Diagnosis

A child presenting with hypotonia at birth needs to be evaluated for sepsis. The most common infections at birth are TORCH infections. Suggestive history and physical examination findings along with serum and urine evaluation are used to confirm such infections.

Certain chromosomal abnormalities such as trisomy 21, Turner syndrome, and Prader-Willi syndrome also present with neonatal hypotonia. Perinatal trauma such as hypoxic-ischemic brain injury and intracranial hemorrhage also is linked with hypotonia at birth. Neuroimaging at birth can aid in establishing this diagnosis.

Arthrogryposis in a newborn who has hypotonia usually is due to lower motor neuron lesions after ruling out sepsis and hypoxic-ischemic encephalopathy. Various metabolic and multisystem diseases also are associated with neonatal hypotonia. Glycogen storage diseases, mitochondrial myopathies, peroxisomal disorders, disorders of carnitine metabolism, and congenital myopathies can be seen as well and can be confirmed by muscle biopsy.

Various neurologic diseases such as spinal muscular atrophy, Charcot-Marie-Tooth disease, Dejerine-Sottas disease, and hereditary sensory and autonomic neuropathy can present with similar symptoms. Electromyography, genetic testing, and muscle biopsy can help in diagnosing these disorders. Neuromuscular junction disorders such as congenital myasthenia should be considered in the differential diagnosis.

## Lessons for the Clinician

Congenital muscular dystrophy can present with neonatal hypotonia, arthrogryposis, feeding difficulties, and failure to thrive. Classic types usually are not associated with any CNS malformations on imaging, and syndromic types typically are associated with brain or spinal cord defects. Muscle biopsy is used to confirm the diagnosis, and once the diagnosis is confirmed, supportive treatments such as physical therapy to improve mobility and contractures, mechanical assistance devices for respiratory difficulties, surgery for orthopedic complications, and social and emotional support for the family must be coordinated. Death is usually due to respiratory causes.

Sehar Ejaz, MBBS, Jacob J. Rosenberg, MD, Satish Kadakia, MD, Nassau University Medical Center, East Meadow, NY

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## **Two-Day-Old Newborn With Failure to Void**

### **Presentation**

A female neonate born at 40 weeks' gestation presents with failure to void for 48 hours. The mother is an 18-year-old primiparous woman who had no significant past medical history or pregnancy complications. Results of prenatal blood tests and ultrasonographic screenings were unremarkable. Maternal screening documented B-positive blood type, rubella immune, negative syphilis screen, negative hepatitis B surface antigen, and positive group B streptococcal screen with adequate treatment during the antepartum period. The infant was delivered via spontaneous vaginal delivery with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The infant was transferred to the newborn nursery for routine newborn care.

Initial vital signs in the newborn nursery were:

Weight, 3,880 g (>90th percentile)

Length, 48.5 cm (25th to 50th percentile)

Head circumference, 34.5 cm (50th to 75th percentile)

Temperature, 98.4°F (36.9°C)

Heart rate, 136 to 148 beats/min

Respiratory rate, 54 to 60 breaths/min

Blood pressure, 66/43 mm Hg

Her initial glucose measurement was 47 mg/dL (2.6 mmol/L). Other than macrosomia, her initial physical examination findings were within normal limits, including normal results of a head, eyes, ears, nose, and throat examination. The lungs were clear to auscultation. Cardiac examination revealed a regular rate and rhythm without murmurs. The abdomen was soft, with normal, active bowel sounds and no palpable masses. Genitourinary examination revealed normal external female genitalia



and a normal-appearing urethral opening. The back and anal examinations revealed no pits, hair tufts, dimples, or vertebral anomalies. The infant had normal proximal and distal tone, with normal primitive and deep tendon reflexes.

She did well throughout her first postnatal day, with her vital signs remaining within normal limits and her glucose values ranging from 59 to 67 mg/dL (3.3 to 3.7 mmol/L). She breastfed well every 2 to 3 hours and passed 5 meconium stools within her first 24 hours. However, she did not void urine.

Due to persistent anuria 24 hours after birth, a urine collection bag was placed on the infant and supplemental formula was encouraged. Her vital signs and physical examination findings continued to remain within normal limits. However, between 36 and 48 hours after birth, she began to develop fussiness, tachycardia, and difficulty feeding. Her temperature was 98.4°F (36.9°C), heart rate was 160 to 180 beats/min, and respiratory rate was 54 to 60 breaths/min. She continued to attempt breastfeeding every 2 to 3 hours, but her mother stated she appeared uncomfortable with feedings, even with bottle supplementation. She continued stooling well, but there still was no documented urine. On physical examination, she appeared fussy and minimally consolable. She had a protuberant abdomen with normal, active bowel sounds. On palpation, her abdomen appeared tender, and a large suprapubic mass could be easily palpated.

Due to failure to void for 48 hours and a suspected distended bladder, bladder catheterization was attempted. The urinary catheter, initially difficult to pass, was placed, and 130 mL of sedimented urine was obtained (normal capacity, 10 to 15 mL). After catheter removal, the infant appeared more comfortable. The abdomen was less distended, and the suprapubic mass had resolved. The infant was returned to the mother for routine newborn care.

On postnatal day 3 (24 hours following bladder catheterization), the infant was again fussy, with a distended abdomen with suprapubic fullness. In the previous 24 hours, she was breastfeeding and tolerating supplemental formula without difficulty and had transitioned from meconium to yellow, seedy stools. However, at the end of postnatal day 3, she still had not voided spontaneously.

A second bladder catheterization removed 75 mL of urine. At that time, an evaluation for failure to void was begun, revealing the diagnosis.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

### *The Diagnosis*

Baseline urine and blood studies showed marginally decreased sodium and carbon dioxide concentrations of 133 mEq/L (133 mmol/L) and 20 mEq/L (20 mmol/L), respectively. Blood urea nitrogen was 11 mg/dL (3.9 mmol/L), and creatinine was 0.6 mg/dL (53  $\mu$ mol/L). Urinalysis results were within normal limits. Renal ultrasonography, obtained after bladder catheterization, revealed a decompressed urinary bladder with normal kidneys with no evidence of hydronephrosis. Voiding cystourethrography (VCUG) showed no vesicoureteral reflux, but the infant did not void following removal of the contrast catheter. A radiograph following the procedure demonstrated a large atonic bladder that raised concern for neurogenic dysfunction. Spinal ultrasonography demonstrated normal cord length, with the tip of the conus medullaris at the level of L1. However, the filum terminale appeared abnormally attached to the posterior wall of the canal at the L3 level and contained a fusiform cystic structure close to the conus.

This study confirmed the diagnosis of occult spinal dysraphism due to the presence of an abnormal filum terminale and tethering of the spinal cord. Interestingly, the infant had no evidence of reflux, hydroureter, or hydronephrosis, thereby suggesting normal urinary function in utero. The infant developed normal urine function on her fifth postnatal day and currently is being monitored closely for recurrence and the development of any other neurologic abnormalities. Also of interest, this patient had none of the physical examination findings that often accompany abnormalities of spinal cord and vertebral development. In most cases of tethered spinal cords, the site of tethering is more caudal, resulting in an elongated cord that terminates at L2–L4. However, in this case, the relationship between proximal cord tethering, normal cord length, sporadic nature of her urinary dysfunction, and the absence of outward physical examination findings is unclear. Per the neurosurgeon's request, magnetic resonance imaging will be obtained at 6 months of age to delineate further the extent of the spinal cord abnormality and need for preemptive repair.

### *Differential Diagnosis*

Failure to void is a relatively uncommon problem in the newborn and can be the initial presentation for a variety of disorders. Approximately 92% of neonates, including preterm and postterm neonates, void within 24 hours of birth, and 99% of neonates void by 48 hours. Any neonate who has not voided spontaneously by 24 hours warrants an evaluation.

A variety of conditions can manifest as failure to void within the first postnatal day, including prerenal, renal, postrenal, and neurologic abnormalities. Prerenal causes can encompass maternal drug ingestion, asphyxia, dehydration, and shock. Among

the intrinsic renal causes are renal agenesis, cystic kidney disease, acquired acute tubular or cortical necrosis, and vascular thromboses. Postrenal causes include any obstructive uropathy of the ureters, bladder, or urethra. Neurologic causes encompass neuropathic bladder dysfunction due to myelodysplasia (open and occult forms of spinal dysraphism), traumatic lesions of the spinal cord, central nervous system tumors, sacrococcygeal teratomas, and anatomic variations associated with imperforate anus.

### *Pathogenesis/Incidence/Natural History*

Occult spinal dysraphism, along with open forms of spinal dysraphism (meningocele, lipomyelomeningocele, or myelomeningocele), termed myelodysplasia, are a group of developmental anomalies that result from defects in neural tube closure. Spina bifida occulta is a closed congenital defect of bony spinal column formation and occurs in up to 30% of the general population. However, in a small subset of this population, abnormalities of spinal cord elements also can be present, and this is termed occult spinal dysraphism. Such abnormalities include tight filum terminale, intradural lipoma, tethered spinal cord, diastematomyelia, and dermal sinuses.

Spinal cord and vertebral formation begins approximately at the 18th day of gestation. Closure of the spinal canal occurs in a cephalocaudal direction and is completed by the 35th day of gestation. The exact cause of spinal dysraphism is unknown, but genetic, environmental, and nutritional factors have been implicated. Increased frequencies of neural tube defects appear to occur in the offspring of mothers who had folic acid deficiency during pregnancy. The overall reported prevalence of spinal dysraphism is 1 per 1,000 live births; the prevalence of occult spinal dysraphism is 1 per 4,000 live births.

Unlike meningocele and myelomeningocele, occult spinal dysraphism appears subtly on physical examination, frequently with only minor physical findings and no obvious motor or sensory abnormalities. More than 90% of affected patients have a cutaneous abnormality overlying the lower spine, such as a mole, hair tuft, dermal vascular malformation, subcutaneous lipoma, or a dimple. It is important to evaluate abdominal musculature, lower extremity function and tone, and anal sphincter tone. In addition, during the abdominal examination, it is important to assess renal size and the presence and degree of bladder distention because the frequency of abnormal lower urinary tract function in patients who have spina bifida occulta, including neuropathic bladder dysfunction, is as high as 40%.

Urologic morbidity rates in patients who have myelodysplasia, specifically spina bifida occulta, are significant. Myelodysplasia can contribute to voiding dysfunction, urinary tract infections (UTIs), vesicoureteral reflux, and renal scarring. In the

neonate, renal ultrasonography, a random evaluation of postvoid residual volumes, VCUG, and urodynamic studies should be considered as the initial radiologic evaluation for neuropathic bladder.

## **Treatment**

Patients who have myelodysplasia, including occult forms, have the potential for a multitude of issues that require frequent monitoring. For this reason, affected neonates require extensive, active, interdisciplinary treatment by trained and coordinated teams beginning in the neonatal period. Neonatology, neurosurgery, urology, orthopedics, neurology, and psychology generally are involved.

The defect initially is repaired shortly after birth and must be monitored for cord tethering or shunt malfunction if a ventriculoperitoneal shunt is placed. Neurosurgic repair is followed by serial examinations of bladder and bowel function, muscle strength, and joint range of motion. Urologic evaluation is necessary to establish a bladder regimen to prevent frequent UTIs and to recognize and treat hydronephrosis or other causes of renal damage that can limit life expectancy. Consultation with a neurologist often is required to delineate neurologic defects and monitor symptom changes. If significant bone abnormalities are present, consultation with an orthopedist may be necessary. In addition, patients should be monitored for appropriate development and be provided with physical therapy, serial developmental evaluations, and psychological support.

## **Lesson for the Clinician**

Although uncommon, failure to void is an alarming but often sentinel clue to underlying pathology in the neonate. It is important to consider both renal and nonrenal causes and evaluate the patient systematically to delineate the abnormality so treatment can be initiated to prevent secondary complications.

Maria N. Kelly, MD, FAAP, Robert S. Hoki, MD, College of Medicine, University of Florida, Gainesville, FL

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# Term Infant With Episodes of Apnea and Bradycardia

## Presentation

A female infant is born by cesarean section at 35 weeks' estimated gestational age to a primigravid woman after a pregnancy complicated by hypertension, gestational diabetes mellitus, and bipolar disorder with a history of suicide attempts. The mother has been off medications for an undetermined amount of time. Her blood type is A+, and results of serologic tests, including group B Streptococcus status, are unremarkable. Delivery was complicated by spontaneous rupture of membranes at 12 hours prior to delivery and variable decelerations. The mother received butorphanol tartrate for pain control. Apgar scores are 8 and 9 at 1 and 5 minutes, respectively.

The infant's birthweight is 2,995 g (50th percentile), length is 48.5 cm (55th percentile), and head circumference is 33.5 cm (55th percentile). The remainder of the physical examination findings are unremarkable. A few hours after birth, the infant begins to have episodes of apnea and bradycardia. Naloxone administration results in no change, and antibiotic therapy is initiated. Results of a complete blood count, chest radiography, and cerebrospinal fluid (CSF) examination are normal. Blood, CSF, and urine cultures are negative. Electroencephalography and electrocardiography results are normal. A computed tomography scan of the head reveals small subarachnoid hemorrhages in the left middle cranial fossa. The infant is intubated and placed on mechanical ventilation with low settings when the apnea does not respond to continuous positive airway pressure and aminophylline. When the clinicians see the baby's father 24 hours later and obtain a brief family history, they determine the diagnosis.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

The initial differential diagnosis in this infant included respiratory suppression due to maternal butorphanol tartrate administration or surreptitious maternal opiate use, infection, apnea of prematurity, seizure, or intracranial hemorrhage. When the father arrived to visit his newborn daughter, clinicians observed that he had a tracheostomy and a diaphragmatic pacer attached to his belt. When questioned about these, the father replied, “I have CCHS. Do you think my daughter might have it too?”

### *The Condition*

Congenital central hypoventilation syndrome (CCHS), also termed Ondine’s curse, is a rare disorder of respiratory control with an estimated incidence of 1 in 200,000 live births. The disorder generally is characterized by a normal respiratory pattern in the awake state and hypoventilation with hypercapnia and hypoxemia during sleep. In more severe cases, the respiratory pattern also is affected while awake. Minute ventilation is decreased by both a decrease in tidal volume and a decrease in respiratory rate. There is a negligible or absent respiratory response to hypercapnia or hypoxemia. In general, neuroimaging does not reveal any central nervous system (CNS) abnormalities. In particular, the brainstem appears to be anatomically normal. There is no other evidence of neuromuscular, pulmonary, or cardiac disease.

Respiratory control involves input from peripheral and central chemoreceptors for hypercapnia and hypoxia to brainstem nuclei that include the pre-Bötzinger complex. This input regulates the activity of an intrinsic oscillator that controls the respiratory pattern. In patients who have CCHS, the response to both types of chemoreceptors is blunted or absent. While awake, cortical input can overcome the blunted response. Affected patients can increase their minute ventilation with exercise but not to the same extent as unaffected people, and older patients may develop feelings of dyspnea with exercise. Although the brain is structurally normal in CCHS, functional magnetic resonance imaging reveals abnormalities, including abnormal neural responses to hypercapnia and hypoxia, based on changes in blood oxygen-dependent signals, in a variety of CNS nuclei.

### *The Diagnosis*

Congenital central hypoventilation syndrome can be diagnosed in a newborn who has hypoventilation in the absence of primary neuromuscular, pulmonary, cardiac, or metabolic disease. Additionally, acquired causes of respiratory control dysfunction, such as hypoxic-ischemic encephalopathy, infection, and CNS hemorrhage or infarction, should be excluded. In this case, making the diagnosis was simplified significantly by the convincing family history. Many cases, however, are sporadic and

may require more extensive evaluation to eliminate other possible causes. A sleep study may be helpful in confirming the diagnosis. Genetic testing also is available.

Congenital central hypoventilation syndrome has been associated with other disorders that involve defective migration or differentiation of neural crest cells. The most common associated disorder is Hirschsprung disease, which occurs in up to 20% of patients who have CCHS. Tumors of neural crest cell origin, including neuroblastoma, ganglioneuroblastoma, and ganglioneuroma, also have been described in those who have CCHS. Such findings suggest that the origin of CCHS may involve neural crest cell abnormalities, but no direct evidence yet supports this hypothesis. Patients who have CCHS have other evidence of autonomic system dysfunction, including heartbeat variability and dysrhythmia, gastrointestinal motility, abnormal pupillary responses, and disorders of sweating and temperature regulation. Thus, although hypoventilation may be the most readily apparent feature of CCHS, autonomic dysfunction may be more widespread than generally appreciated.

## **Genetics**

Most cases of CCHS are sporadic, although familial cases have been described. There also are reports of increased autonomic dysfunction in the parents of affected patients. Congenital central hypoventilation syndrome is inherited in an autosomal dominant pattern. The most commonly mutated gene is the *PHOX2B* gene, accounting for more than 90% of the identified mutations. *PHOX2B* is a member of the paired-like homeobox gene family and is characterized by two polyalanine repeat regions. The most common mechanism for mutation involves expansion of the polyalanine repeat in exon 3. The expansion is inherited in a stable fashion. Frameshift, nonsense, and missense mutations also have been described. Genotype and phenotype appear to correlate, with the most severe disease associated with a greater increase in the number of polyalanine repeats. The severity of respiratory symptoms and the risk of Hirschsprung disease and neural crest tumors are greater in the nonpolyalanine repeat mutations. Mice heterozygous for a targeted mutation in the *PHOX2B* gene demonstrate a blunted response to hypoxia and hypercapnia compared with wild-type mice and abnormal development of chemoreceptors. Although significantly less common, mutations in the *RET*, *GDNF*, *EDN3*, *BDNF*, and *ASCL1* genes also have been identified in patients who have CCHS.

## **Management**

Management is targeted to prevent hypercapnia and hypoxemia. Some form of mechanical ventilation is required because supplemental oxygen alone is not adequate to prevent hypoventilation with hypercapnia and the subsequent development of pulmonary hypertension. A variety of mechanical ventilation strategies have been



used, including positive-pressure ventilation through a tracheostomy and bilevel positive-pressure ventilation through a face mask. Diaphragm pacing via electronic stimulation is another option and affords greater portability, allowing for at least some periods of time free from mechanical ventilation. Respiratory stimulants, such as caffeine, have no role in the management of CCHS.

## Outcome

Congenital central hypoventilation syndrome is a lifelong disorder that requires life-long respiratory support. With attention to care, most affected patients survive into adulthood. Neurodevelopmental outcomes of affected children vary widely, but the average child has some degree of neurodevelopmental delay. This may be the result of intermittent episodes of hypoxia, but a primary effect of the mutation on cognitive ability cannot be excluded. A gastrostomy to insure adequate nutrition also is not uncommon, particularly in the newborn period.

## Lesson for the Clinician

Common causes of apnea include prematurity, infection, intracranial hemorrhage, and metabolic disorders. Eliciting a family history remains a useful and time-tested modality of clinical investigation, as illustrated by this case.

Akshaya Vachharajani, MD, Washington University School of Medicine, St Louis, MO; Sarah Kuhlman, MD, CoxHealth, Springfield, MO.; Brian Hackett, MD, Washington University School of Medicine, St Louis, MO

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**COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER**

Extensive *PHOX2B* genotyping of CCHS has led to targeted anticipatory management of affected patients. For example, while all affected patients, regardless of genotype, require annual Holter monitoring to assess for sinus pauses, chest and abdominal imaging to assess for neural crest tumors is recommended only for patients with a specific genotype. Early diagnosis, targeted anticipatory management, and timely, effective treatment have dramatically improved neurocognitive outcomes and life expectancy.

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## **Two-Month-Old With Episodic Body Contractions**

### **Presentation**

A 2-month-old male baby is admitted to the hospital for the third time with a history of abnormal movements since the first day after delivery. He returns to the hospital on this occasion due to the appearance of bluish skin associated with the occurrence of abnormal movements that persist despite the use of anticonvulsant medication.

The parents describe the abnormal movement as a sudden, startling jump followed by a forceful body contraction in which the baby becomes rigid, with fists firmly clenched, arms flexed, spine erect, head tilted slightly backward, and legs extended. He remains awake during and after the episode. The contraction lasts for approximately 10 seconds and is followed by floppiness for 1 to 2 seconds. Sometimes episodes are accompanied by a bluish coloration of the entire body. Startling sounds or even a sudden touch trigger the episodes, which occur frequently all day long. They explain that firm holding and hugging sometimes seem to stop the episodes.

On questioning, they report no eye rolling, blinking, or lip smacking during the episodes, and the episodes usually are not preceded by feedings. The boy has good suckling and appetite; has no constipation or diarrhea; and is active, afebrile, and seemingly otherwise healthy.

A review of the pregnancy and delivery reveals no complications or infections during the pregnancy, although the mother says that the movements of the baby in the womb seemed different from those in previous pregnancies. At birth, the infant aspirated meconium, with associated respiratory distress. Apgar scores were 7 at 1 minute and 9 at 5 minutes. The infant was admitted to the neonatal intensive care unit (NICU) due to respiratory distress and received ampicillin and gentamicin, but he did not require intubation or blood transfusion.

Cultures of cerebrospinal fluid (CSF), blood, and urine were negative. ABO incompatibility was associated with indirect hyperbilirubinemia, which resolved with phototherapy.

He began having abnormal movements in the NICU, but results of electroencephalography (EEG), neurosonogram, and brain computed tomography (CT) scan were normal. He was discharged from the hospital with a prescription for oral phenobarbital. He was readmitted a few days later due to the persistence of symptoms, but EEG, brain CT scan, and metabolic test results still were normal. On subsequent hospital discharge, oral phenytoin was added to the anticonvulsant regimen.

There is no history of convulsive disorder in the family or any other significant disease in the parents and siblings.

On physical examination, the baby is awake and active, and vital signs are normal. He startles in reaction to clapping of the hands and tapping over the patellar tendon. The startle reaction is exaggerated, characterized by a jump followed by a generalized muscular spasm, with clenching of the fists, flexion of the arms, erection of the spine, and extension of the legs. As reported by the parents, there is no lip smacking, rolling of the eyes, or blinking. The episodes last a few seconds and can be stopped with forced flexion of the head and legs over the trunk. If the episodes are not stopped, the baby's face turns cyanotic. He exhibits hypertonia during episodes.

His head circumference is 34 cm, and the fontanelles are neither bulging nor sunken. He has no hypo- or hyperpigmentation of the skin, no hemangiomas, and no skin lesion. There is no palate deformity or dysmorphic facies. The heartbeat is regular without a murmur. Breath sounds are normal, with bilateral clear lung auscultation. The abdomen is not distended, and there is an umbilical hernia. There is no acrocyanosis. Testicles are descended with hydrocele.

Neurosonography reveals no subependymal or intracranial hemorrhage, and periventricular echogenicity is normal. Results of head CT scan, brain magnetic resonance imaging (MRI), and EEG are normal. Blood culture is negative at 5 days, urine culture is negative at 48 hours, and results of urinalysis are within normal limits. Two measurements of ammonia are 34.3 mcg/dL (48 mcmmol/L) and 28.0 mcg/dL (20 mcmmol/L), glycine is minimally increased, lactic acid measurements are 31 mg/dL (3.4 mmol/L) and 0.6 mg/dL (0.07 mmol/L), pyruvic acid is less than 0.1 mg/dL (11.4 mcmmol/L), total carnitine is 54 mcmmol/L, and free carnitine is 54 mcmmol/L. An HIV-1 enzyme-linked immunoassay test result is negative, and the infant's blood type is B+.

The clinical findings coupled with the generally negative laboratory tests suggest the diagnosis.

## Discussion

### *Differential Diagnosis*

Tonic seizure is suggested by stiffening of muscles in this case, but there is no EEG abnormality, and tonic seizures are not sensory induced. The seizures being induced by unexpected stimuli and a startle response followed by a tonic phase suggest the possibility of startle seizure, but there are no corresponding EEG abnormalities. Stiffening of the body also occurs in infantile spasm, but such spasms are not sensory induced.

*Take a moment to consider the diagnosis in this infant.*

### *Diagnosis*

Hyperekplexia is a nonepileptic disorder characterized by an exaggerated startle response and generalized muscular rigidity triggered by sensory stimuli. It is also known as stiff baby syndrome or startle disease.

Clinical manifestations can appear early in the prenatal period as abnormal intra-uterine movements. In the postnatal period, it presents with increased muscle tone that may predispose to hernias and abnormal movements consisting of tonic spasms and myoclonus that may be associated with episodes of apnea. The clinical hallmark is flexor spasm induced by nasal bridge tapping.

The pathophysiology of hyperekplexia is impaired function of inhibitory neurotransmitters (glycine/gamma-aminobutyric acid) related to glycine chloride channel mutation or autoimmune-mediated damage of glutamic acid decarboxylase.

Because hyperekplexia is not characterized by epileptiform discharges or structural brain anomaly, EEG, brain CT scan, and brain MRI yield normal findings. Nonetheless, electromyography discloses almost permanent muscular activity.

Among the complications are hernias, discomfort, and pain due to the hypertonic state, with episodes of apnea during tonic spasms that may be life-threatening. Mental retardation also may be associated with hyperekplexia.

The hypertonia may ameliorate spontaneously with increasing age, but it also may recur in adult life. Persistence of the exaggerated startle response may continue through adulthood, leading to falls. Delayed motor development may be seen.

This chronic condition has no cure and may alter the patient's lifestyle. Medical management is directed toward decreasing muscle tone with administration of clonazepam and forced flexion of the head and legs toward the trunk when the patient experiences the abnormal movement.

## Lessons for the Clinician

Hyperekplexia is not a particularly common diagnosis, but knowing the features of its clinical presentation may enable the clinician to differentiate this disorder from epileptic disorders that may seem similar. Hyperekplexia should be considered in patients who experience abnormal movements triggered by sensory stimuli and in whom a tonic spasm can be elicited by tapping the nasal bridge. Other potential clues are stopping of the abnormal movements by maneuvers such as forced flexion of head and legs toward the trunk; normal results on CSF analysis, EEG, brain CT scan, and MRI; and the presence of umbilical hernias due to hypertonicity and abnormal movements. Management involves knowing the maneuver that stops the spasm and, thus, prevents the associated apnea due to forceful tonic spasms.

*Ileana M. Arbona, MD, Tania Diaz, MD, Jenaro Scarano, MD, Department of Pediatrics, Saint Luke's Memorial Hospital, Ponce, Puerto Rico*

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## **A Term Newborn Who Has a Sacral Mass**

### **The Case**

A term newborn presents with a sacral mass.

#### ***Prenatal History***

- 23-year-old gravida 3 para 2002 Hispanic mother
- Estimated gestational age: 39 4/7 weeks
- Blood type O+, antibody screen-negative, rubella immune, hepatitis B surface antigen-negative, venereal disease research laboratory test-nonreactive, chlamydia-negative, group B Streptococcus screen-negative,  $\alpha$ -fetoprotein-negative
- Pregnancy complicated by migraine headaches, treated with hydrocodone/acetaminophen and promethazine
- Spontaneous rupture of membranes approximately 10 hours prior to delivery; clear amniotic fluid

#### ***Birth History and Presentation***

The infant was delivered via precipitous spontaneous vaginal delivery. He cried spontaneously, was placed under a radiant warmer, and was dried and stimulated. Apgar scores were 8 at 1 minute and 9 at 5 minutes. A soft sacral mass, completely covered with skin, was noted immediately (Figure 43.1). His birthweight was 3,540 g.





**Figure 43.1.** Full-term newborn with a sacral mass that is skin-covered.

## ***Case Progression***

### ***Vital Signs***

- Heart rate, 136 beats/min
- Respiratory rate, 48 breaths/min
- Blood pressure, 58/35 mm Hg
- Temperature, 97.9°F (36.6°C)

### ***Physical Examination***

- Head: Normocephalic; normal, open, flat fontanelles; symmetric facies; patent nares; intact palate
- Lungs: Clear, equal breath sounds; unlabored respirations
- Cardiovascular: Normal S1, S2; regular rate and rhythm; no murmurs or gallops
- Abdomen: Nondistended, soft, nontender; no organomegaly
- Genitourinary: Normal term male genitalia; testes descended bilaterally; patent anus
- Skeletal: Soft, fluid-filled sacral mass,  $3 \times 5 \times 1.5$  cm
- Skin: No icterus, birthmarks, or rashes
- Neurologic: Alert and active; normal suck; symmetric Moro; normal strength and tone; deep tendon reflexes 2+ in lower extremities; symmetric movements bilaterally

### ***Laboratory Evaluation Performed at the Level II Nursery***

- White blood cell count,  $24.4 \times 10^3/\text{mcL}$  ( $24.4 \times 10^9/\text{L}$ )
- Hematocrit, 52.5% (0.525)
- Platelet count,  $182 \times 10^3/\text{mcL}$  ( $182 \times 10^9/\text{L}$ )
- Manual differential count:
  - 61% segmented neutrophils
  - 1% banded neutrophils
  - 31% lymphocytes

### ***Imaging Studies Performed at the Level II Nursery***

- Spinal radiographs: 12 pairs of ribs; intact vertebral bodies
- Sacral ultrasonography: Septated cystic mass

The infant subsequently was transported to the tertiary care center for further evaluation of the sacral mass.

### ***Differential Diagnosis***

#### ***Term Infant Who Has a Sacral Mass***

Caudal regression syndrome

Congenital ependymoblastoma/ependymoma

Congenital spinal hamartoma

Human tail lipoma

Lipomyelomeningocele

Myelocystocele

Myelomeningocele

Sacroccygeal teratoma

*Take a moment to consider the diagnosis in this infant.*

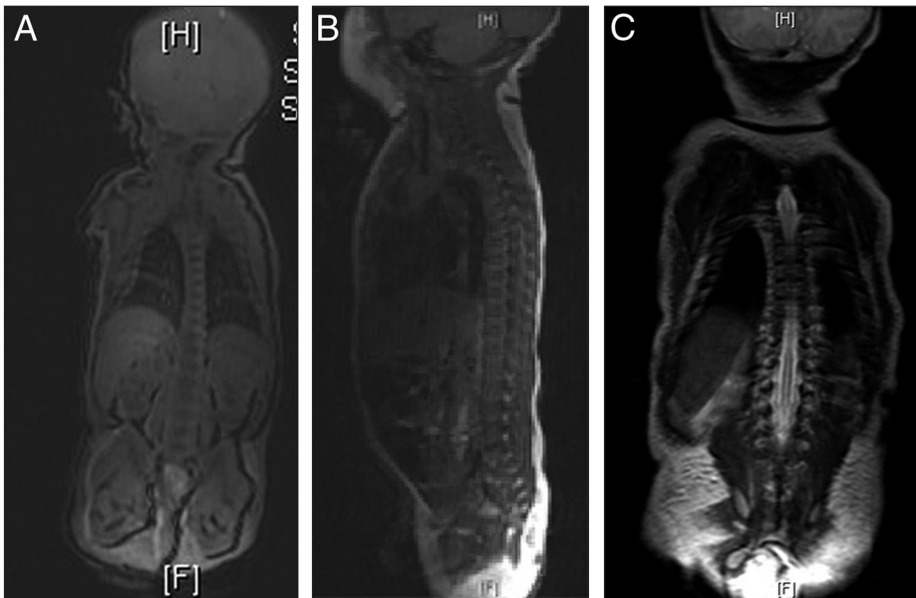
## Actual Diagnosis

### *Lipomyelomeningocele*

Soon after arrival at the tertiary care center, the infant was seen by the neurosurgery service. Magnetic resonance imaging (MRI) was recommended as well as consultation by the urology service.

### *Diagnostic Studies*

- Magnetic resonance imaging of brain: Normal
- Magnetic resonance imaging of spine (Figure 43.2) with gadolinium: Spinal cord elements extending inferiorly to at least the upper sacral levels. A dorsal neural arch defect involving the lower sacral region, with a lipoma extending at least to the subcutaneous location. A likely cerebrospinal fluid (CSF) tract or a meningocele at this site. Mild prominence of the central canal rather than a split cord as well as a prominent terminal ventricle.
- Renal ultrasonography: Normal
- Voiding cystourethrography: No vesicoureteral reflux



**Figure 43.2.** Spine magnetic resonance imaging with gadolinium showing spinal cord contents extending inferiorly to at least the upper sacral levels. There is also a dorsal neural arch defect involving the lower sacral region with a lipoma.

The infant was discharged on postnatal day 6, with normal feeding, stooling, and voiding. Plans were made for him to be seen in the neurosurgery clinic approximately 6 weeks later for a follow-up spinal MRI to determine if surgical intervention was required.

## The Experts

The term spinal dysraphism includes a group of defects derived from maldevelopment of the ectodermal, mesodermal, and neuroectodermal tissues. Spinal dysraphism is classified into open (spina bifida aperta) and closed (spina bifida occulta) defects. Lipomyelomeningoceles (also referred to as spinal lipomas) constitute approximately 35% of occult spinal dysraphism and 20% of skin-covered lumbosacral masses.

## Embryology

Lipomyelomeningoceles are occult dysraphic states consisting of a partial dorsal myeloschisis with lipoma fused to the dorsal aspect of the open spinal cord. One embryologic theory suggests that if the ectoderm undergoes premature disjunction from the neural tube, mesenchyme can migrate into contact with the inside of the forming neural tube. The inside of the neural tube that normally is not in contact with the mesenchyme induces the mesenchyme to differentiate into fat. The outside of the neural tube induces the mesenchyme to form the normal pia arachnoid and dura and normal subarachnoid spaces to form ventral to the neural plate. The ectoderm fuses dorsally, with the skin subsequently covering the underlying defect.

## Prenatal Diagnosis

Spina bifida is detectable in utero with ultrasonography. Because this is a closed neural tube defect, the maternal serum  $\alpha$ -fetoprotein concentration may not be elevated. Specific ultrasonographic findings that are considered characteristic of neural tube defects include a “lemon”-shaped bony calvarium caused by scalloping of the frontal bones and the “banana sign” that results from flattening of the cerebellar hemispheres and elimination of the cisterna magna. However, most prenatally diagnosed lipomyelomeningoceles appear normal on head ultrasonography, making prenatal diagnosis more challenging. Therefore, to detect these anomalies, it is important not only to scan the fetal head but also to image the fetal spine in the lumbosacral region.

## Postnatal Presentation

It may be difficult to differentiate between open and closed defects prenatally; many experts recommend a conservative approach of elective cesarean delivery rather than vaginal delivery. Lipomyelomeningocele is the most common form of

spinal lipoma, it predominates in females, and it is located most frequently in the lumbosacral region. Presentation is either clinically evident as a skin-covered mass or develops as a slowly progressive neurologic syndrome that includes sensory and motor deficits over and below the involved area plus bladder dysfunction. Some cutaneous markers may signal the presence of underlying occult spinal dysraphism (Table 43.1).

**Table 43.1. Cutaneous Lesions Associated With Spinal Dysraphism**

High Index of Suspicion	Low Index of Suspicion
Hypertrichosis	Telangiectasia
Large sacral dimple (>2.5 cm from anal verge)	Capillary malformation (port-wine stain)
Acrochordans/pseudotails/true tails	Hyperpigmentation
Lipomas	Melanocytic nevi
Hemangiomas	Small sacral dimple (<2.5 cm from anal verge)
Aplasia cutis or scar	Teratomas
Dermoid cyst or sinus	

Adapted from Drolet BA, Conlon JD. Developmental abnormalities. In: Eichenfield LF, Frieden IJ, Esterly NB, eds. *Textbook of Neonatal Dermatology*. Philadelphia, PA: Saunders; 2001:123.

## Management

Infants and children who have cutaneous stigmata of dysraphism require a careful neurologic examination and thorough urologic evaluation. Ultrasonographic examination of the distal spine and lipoma often can delineate the lipoma and spinal dysraphism. Plain-film radiography may show segmentation errors of the vertebral bodies (hemivertebrae, fused vertebrae), increased lumbar lordosis, or partial agenesis of the sacral spine. Magnetic resonance imaging is most helpful in planning a surgical approach because it allows direct visualization of the neural plate, the orientation of the plate within the canal, and its orientation with respect to the lipoma.

## Clinical Outcome

The prognosis for the infant who has a skin-covered lesion is very good if appropriate care is provided early. Neonatal resection of congenital lipomatous tumors is necessary to prevent tethering of the spinal cord that might lead to irreversible neurologic damage if not released. Several series have documented the successful and safe untethering of spinal cords from lipomas, with minimal morbidity and mortality. In one report, 20% of patients who underwent resection in the neonatal period required subsequent surgery for retethering, suggesting the need for close follow-up.

Kristine B. Boyle, RNC, MS, NNP, Stanford University Medical Center, Stanford, CA; and JoDee M. Anderson, MD, Oregon Health & Science University, Portland, OR

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### COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER

Fetal MRI has improved the prenatal detection rate of closed neural tube defects.

**FOLLOW-UP COMMENTARY BY DR KRISTINE BOYLE, STANFORD UNIVERSITY MEDICAL CENTER**

The infant was discharged home at 5 days of age with a diagnosis of myelocystocele versus lipomyelomeningocele.

He was then seen at 6 weeks of age in the Neurosurgery Clinic, at which time a urology consult was recommended. At that time, the infant was reportedly doing well with no acute neurologic concerns. He was moving all extremities well and had normal bowel and bladder patterns. The sacral mass was felt to be stable with no change in size.

He was then seen in the High-Risk Infant Follow-Up Clinic at 5 months of age and was noted to have normal growth and a normal neurologic exam. His development was felt to be close to his chronologic age.

Magnetic resonance imaging of the spine performed at 5½ months of age revealed a lumbosacral lipomyelomeningocele. The subcutaneous dorsal lipoma was seen overlying S3. There was a very-low-lying conus ending in the sacrum. Spinal cord elements and components of the lipoma and CSF extended into the mass at approximately the level of S3. A finding of low-lying cerebellar tonsils was also noted.

At 7½ months of age, the infant underwent surgical repair including a lumbosacral laminectomy and intradural microdissection with repair of tethered cord and ligation of the terminal dural sac below the spinal cord (meningocele sac extending into large subcutaneous sacral lipoma). He was discharged home on postop day 3 without complications.

He was seen in the urology clinic at 9 months of age, where a renal bladder ultrasound was normal and he was doing well and developing normally. Urodynamic studies revealed probable reflux bladder, which is normal for his age. Serial renal bladder ultrasounds have shown normal kidney development and no hydronephrosis.

The patient began walking at 14 months and otherwise was meeting his milestones appropriately and developing normally without any neurologic or urologic concerns. He has had no urinary tract infections.

In a visit at about 27 months of age, it was noted that the patient had a severe delay in language development. He began speech and language therapy. An audiology exam at that time revealed normal hearing.

A follow-up MRI was performed at 8½ years of age and demonstrated stable, low-lying cerebellar tonsils at approximately 6–7 mm below the foramen magnum, as well as a small hydromyelia at T3–T4.

The patient continues with regular follow-up with neurosurgery and urology. He was referred to plastic surgery for evaluation and possible removal of his residual lipoma.

## Neural Tube Defect in Infant of Epileptic Mother

### Presentation

A 37-week female infant is born via cesarean delivery due to preeclampsia to a 26-year-old G1 mother. All maternal serologic test results are within normal limits. The pregnancy was complicated by maternal primary generalized epilepsy treated with valproic acid (VPA) and supplemented with folic acid, mild thrombocytopenia attributed to VPA therapy, and increased maternal serum  $\alpha$ -fetoprotein level at 17 weeks. Antenatal ultrasound reveals a lumbosacral myelomeningocele and Chiari II malformation.

After birth, the infant is noted to have a midline sacral defect and is positioned side lying. She has mild respiratory distress that improves with continuous positive airway pressure. Apgar scores are 7 and 8 at 1 and 5 minutes, respectively. She is transitioned to a high-humidity nasal cannula and transported to the neonatal intensive care unit for further management.

On physical examination, the patient's birthweight is 2.79 kg (25th percentile), length is 51 cm (90th percentile), and head circumference is 29.5 cm (<3rd percentile). She has close-set eyes, a prominent glabella, and epicanthal folds. Her ears are normal in size and position. Her anterior fontanelle is slightly full, with sagittal sutures splayed 1 cm. Her palate is intact, with gag and suck present. Her heart has a regular rate and rhythm with no murmur appreciated. Pulses and perfusion are normal, and breath sounds are clear with moderate aeration. Her abdomen is soft, nontender, and nondistended, with no hepatosplenomegaly. She has spontaneous movement bilaterally at her hips, knees, and ankles. Her spinal defect is located over the lumbosacral area and is 2 cm  $\times$  1 cm, with moist reddish-purplish tissue. A 1-cm rim of hemangiomatous tissue is present at the superior and lateral aspects of the lesion. The patient has normal Tanner 1 female genitalia. Anus is patent with anal wink reflex present. She has long thumbs bilaterally and low-set, inverted, and widely spaced nipples.



## Discussion

### ***Diagnosis and Course***

A postnatal head ultrasound confirms the antenatal suspicion of Chiari II malformation and shows mild ventriculomegaly. A skeletal survey reveals hypoplastic thenar eminences, lumbosacral dysraphism, and lacunar (Luckenschadel) skull. Echocardiogram reveals a large perimembranous ventricular septal defect (VSD) and a moderate secundum atrial septal defect (ASD). Abdominal and renal ultrasounds are unremarkable.

*Take a moment to consider the diagnosis in this infant.*

These findings of myelomeningocele with associated Chiari II malformation, VSD, ASD, and minor craniofacial and skeletal anomalies are consistent with fetal valproate syndrome (FVS).

### ***The Condition***

Fetal valproate syndrome is a well-recognized pattern of malformations that results from prenatal exposure to valproic acid (Depakote®, Abbott Laboratories, Abbott Park, IL) and consists of major and minor anomalies, characteristic facial features, central nervous dysfunction, and altered physical growth. Valproic acid is metabolized by the liver and readily crosses the placenta; it increases levels of gamma-aminobutyric acid in the brain. In utero exposure to VPA was first associated with neural tube defects (NTDs) in 1982,<sup>1</sup> and additional associated anomalies were described in 1984.<sup>2</sup>

Valproic acid exposure during pregnancy is associated with a 10% to 11% risk of major anomalies, including most classic NTDs, as well as cardiac, musculoskeletal, and craniofacial defects.<sup>3,4</sup> Neural tube defects occur in 1% to 2% of exposed infants<sup>1</sup> and are generally more severe and more likely to be associated with hydrocephalus and midline defects than idiopathic NTDs.<sup>4</sup> The most commonly associated cardiac defects are ventricular septal defect, aortic stenosis, pulmonary stenosis, and patent ductus arteriosus; they are diagnosed in one-quarter of patients who have FVS. Musculoskeletal manifestations are present in the majority of affected infants and are variable, ranging from nail hypoplasia to more severe radial and thoracic cage defects. Long, thin, overlapping fingers and toes are most commonly described, although contractures and thumb abnormalities may also be present. Craniofacial abnormalities include a small, broad nose with a flattened nasal bridge; long philtrum with thin upper lip; epicanthal folds; hypertelorism; high forehead; small, low-set ears; and micrognathia. Other less commonly associated anomalies include genital defects (hypospadias and undescended testes), pulmonary hypoplasia, cleft palate, omphalocele, and ocular abnormalities (esotropia, nystagmus, and microphthalmia). Limited information exists regarding long-term outcomes for children

who have FVS. Mortality during infancy is ~10% and associated with multiple congenital defects, especially cardiac related. Surviving infants are at risk for speech and motor delay (20% to 28%) and cognitive impairment (10%), as well as attention-deficit and autistic spectrum disorders.

Valproic acid is teratogenic to most animal species, but the human embryo seems to be most susceptible.<sup>3</sup> Proposed mechanisms of VPA teratogenicity include folic acid deficiency, oxidative stress, and inhibition of histone deacetylases that result in altered gene expression. Recurrence risk for FVS among women who continue to take VPA during subsequent pregnancies is estimated at 55%;<sup>5</sup> this elevated risk is likely due to predisposing maternal genetic factors<sup>6</sup> and/or intrinsic abnormalities of VPA metabolism.<sup>4</sup> Teratogenic effects are most closely related to first-trimester dosing, with a higher risk of malformations (especially NTDs) associated with larger daily VPA doses (>800 to 1,000 mg/day) and antiepileptic polytherapy.<sup>7</sup> However, uncontrolled epilepsy during pregnancy can be harmful to both mother and fetus, and withdrawing an antiepileptic agent during pregnancy is not recommended. Changes to antiepileptic therapy should be attempted before conception, and antiepileptic therapy should be prescribed to minimize risk to the mother and fetus. Women should generally be treated with monotherapy, with the lowest possible dose divided 2 to 3 times per day to minimize serum level fluctuations, and women should receive additional folic acid supplementation before conception and throughout pregnancy.<sup>3,8</sup>

### **Case Progression**

The infant's lumbosacral myelomeningocele was repaired 2 days after birth. A ventriculoperitoneal shunt was placed 2 weeks after birth for progressive ventriculomegaly. She has always voided and stoolled spontaneously. The genetics service was consulted and confirmed the diagnosis of FVS. A chromosomal microarray revealed no clinically relevant genomic imbalance. The patient has an ASD and a muscular VSD that has almost completely closed spontaneously. She is followed up in the multidisciplinary spina bifida clinic and by cardiology and neurosurgery.

### **Lessons for the Clinician**

Fetal valproate syndrome should be considered in any infant exposed in utero to valproic acid. An exposed newborn should be evaluated specifically for neural tube defects as well as for cardiac, musculoskeletal, and craniofacial defects. A multidisciplinary care team may be needed for a child who has FVS.

*Douglas Moeckel, MD, D. Kathy Grange, MD, Jennifer A. Wambach, MD, Washington University School of Medicine in St Louis and St Louis Children's Hospital, St Louis, MO*

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*Part 12*

# **Otolaryngology**

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## Masses in the Oral Cavity

### The Case

A 36+1-week female newborn has masses arising from the oral cavity.

#### *Prenatal History*

- 21-year-old G3P1 woman who had good prenatal care
  - Prenatal laboratory evaluation: blood type AB-negative, rubella-immune, venereal disease research laboratory–nonreactive, hepatitis B surface antigen-negative, group B Streptococcus-negative
- Because of a history of previous miscarriages, the mother received progesterone until 13 weeks' gestation and had multiple prenatal ultrasonographic examinations (normal at 6, 9, 12, 20, 25, and 34 weeks)
- Pregnancy complicated by hyperemesis gravidarum (treated with ondansetron), urinary tract infections (treated with nitrofurantoin), and late-onset pregnancy-induced hypertension
- No alcohol, tobacco, or other substance use

#### *Birth History*

- Labor induced at 36 weeks' gestation for symptomatic pregnancy-induced hypertension
- Hand/arm presentation noted at membrane rupture prompted delivery via primary cesarean section
- Unexpected finding of a large, multilobulated mass arising from the infant's oral cavity (Figures 45.1 and 45.2) at birth
- Despite the mass, the infant responded well to stimulation, with no respiratory distress or airway compromise
- Apgar scores of 8 at 1 minute and 9 at 5 minutes
- Birthweight: 2,420 g



**Figure 45.1.** Photograph at 2 days of age shows a large mass arising from the infant's oral cavity. Two smaller masses also in the oral cavity are obscured by the larger mass.



**Figure 45.2.** Side view of the mass.

## **Case Progression**

### ***Physical Examination***

Initial examination revealed an appropriate-for-gestational-age female infant. Aside from the large mass protruding from her oral cavity, she did not appear dysmorphic. A careful oropharyngeal examination revealed that the firm, nontender,  $3 \times 4$ -cm, multilobulated, pedunculated mucosal mass arose from the left maxillary alveolus on a vascular stalk (Figure 45.3). A separate  $2 \times 2$ -cm bilobed mass arose from the left mandibular alveolus but did not protrude out of the mouth (Figure 45.4). The posterior oropharynx was obscured by the mass, but the infant had no respiratory distress to suggest airway obstruction. The presenting left arm and hand were slightly bruised. The remainder of the physical examination findings were normal.



**Figure 45.3.** Intraoperative photo showing the tumor attachment via a vascular stalk to the maxillary alveolus.



**Figure 45.4.** Intraoperative photo showing the presenting mass and a separate, bilobed mass originating from the mandibular alveolus.

Maintenance intravenous fluids were started. A Telfa™ pad (Kendall, Mansfield, MA) moistened with saline was applied to the protruding mass to prevent desiccation. Over the course of 1 hour, focal areas of the mass darkened, suggesting some vascular insufficiency. No bleeding was observed, but a complete blood count, coagulation panel, and blood type and screen were ordered as a precaution.



***Laboratory Studies***

White blood cell count:  $12.5 \times 10^3/\text{mcL}$  ( $12.5 \times 10^9/\text{L}$ ), 31% neutrophils, 3% bands, 50% lymphocytes

Hemoglobin: 13.6 g/dL (136 g/L)

Hematocrit: 40.4% (0.4)

Platelet count:  $192 \times 10^3/\text{mcL}$  ( $192 \times 10^9/\text{L}$ )

Prothrombin time: 11.3 seconds

Partial thromboplastin time: 40 seconds

Fibrinogen: 161 mg/dL (4.7 mmol/L)

International normalized ratio: 1.1

The infant was transferred to a tertiary neonatal intensive care unit for surgical evaluation.

***Differential Diagnosis******Masses in the Oral Cavity***

Bohn nodules

Epulides

Hemangiomas

Mucocele

Myofibromas

Papillomas

Ranulas

Rhabdomyomas

Sarcomas

Teratomas

*Take a moment to consider the diagnosis in this infant.*

## **Actual Diagnosis**

### ***Multiple Congenital Epulides***

## **The Experts**

Congenital epulis (plural: epulides) is a benign tumor arising from the oral cavity of newborns. Initially described in 1871 by Neumann, this condition is rare, with only 186 published cases found in a literature review by Yavuzer, Ataoğlu, and Sari in 2001.<sup>1</sup> The tumor presents as a firm, fleshy, nontender, multilobed, pedunculated mass attached to either the maxillary or mandibular alveolar ridge (3:1 maxillary preponderance) by a vascular stalk.<sup>2</sup> Extremely rare extra-alveolar cases have involved the tongue.<sup>3</sup> Masses as large as 9 cm have been described. Although the typical presentation is a solitary tumor, approximately 10% of all published cases report multiple tumors, as in this case. There is an 8:1 female-to-male presentation.<sup>4</sup>

The differential diagnosis of an intraoral mass is extensive. The location in the mouth, structure from which a mass arises, and size and appearance of the mass are important in narrowing the differential diagnosis. Mucocoeles are common cystic masses arising from extravasation of saliva into soft tissue from ruptured salivary ducts. They are found on the inner lips, cheeks, underside of the tongue, or floor of the mouth (where they are referred to as ranulae). Bohn nodules are common white keratinous eruptions classically found on the alveolar ridges, but they rarely grow to the size of the masses in this infant. A large hemangioma can appear similar to congenital epulis, but hemangiomas usually arise from the lips and are not pedunculated. Papillomas associated with human papillomavirus infection can present as a pedunculated mass in the mouth arising from the lips, cheeks, or tongue. However, they do not typically present in the immediate postnatal period and have characteristic fingerlike projections. Other rare tumors (rhabdomyoma, sarcoma, myofibroma, teratoma) cannot be definitively distinguished from congenital epulis without histologic analysis.

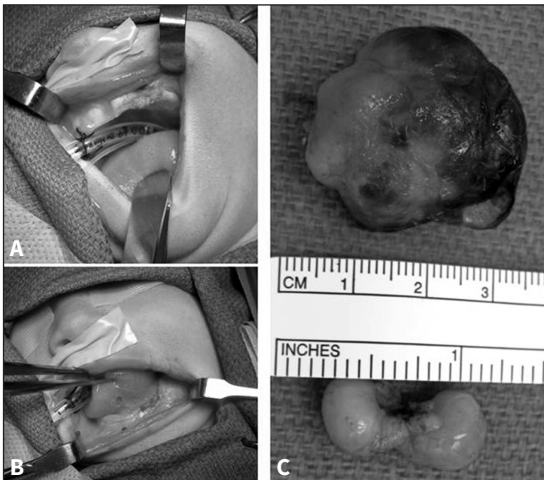
The cause of congenital epulis is unclear. Under light microscopy, the tumor is strikingly similar to granular cell tumors, with sheets of large eosinophilic polygonal cells that have small basophilic nuclei. However, there are important clinical differences. Congenital epulis affects only neonates, preferentially affects the gingiva, and has no malignant potential. Granular cell tumors occur in all age groups, rarely affect the gingiva, and have malignant potential. There are also significant immunohistochemical differences. Unlike granular cell tumors, which stain strongly for S-100 protein due to their neural crest origin, congenital epulis rarely stains positively for S-100 protein. No characteristic immunohistochemical profile has been found for

congenital epulis. Epithelial, fibroblastic, myoblastic, histiocytic, odontogenic, and mesenchymal origins have all been proposed, but the precursor cell for congenital epulis remains unknown.

Because of its female predilection, rapid in utero growth, and tendency to stop growing after birth, a hormonal mechanism has been proposed. Interestingly, the mother of this infant had taken progesterone until 13 weeks' gestation for a history of miscarriages. However, estrogen or progesterone receptors are not found in congenital epulis, arguing against this connection.

Although spontaneous regression has been described in smaller masses, larger masses may interfere with breathing or feeding and require resection. In this case, the lack of respiratory compromise reinforced that air flow is predominantly via the nose rather than the mouth in neonates.

The infant underwent surgical excision of the maxillary and mandibular epulides with electrocautery under general endotracheal anesthesia (Figures 45.3, 45.4, and 45.5). Due to the size of the primary mass, intubation was facilitated with a video laryngoscope. During surgery, a third, 0.7-cm right maxillary epulis was found but not excised because of the benign nature of the mass and the tendency to regress. Surgical specimens were sent to pathology for analysis, which confirmed the diagnosis of congenital epulides. The infant was extubated and started on ad lib feedings on postoperative day 1 and discharged from the hospital on postoperative day 2.



**Figure 45.5.** Postoperative photos after tumor excision with electrocautery. Gross specimens are seen on the right.

At her follow-up appointment with the pediatric otolaryngologists 1 month after discharge, her maxillary and mandibular alveolar ridges were well healed, with no recurrence of the two excised epulides. The third unexcised right maxillary epulis measured 0.5 cm.

Although the mother had multiple two-dimensional ultrasonographic evaluations during her pregnancy, the parents also paid for several elective three-dimensional fetal ultrasonography images at 16, 24, and 32 weeks' gestation for keepsake purposes. Reexamination of the 32 weeks' gestation three-dimensional image revealed the protruding epulis (Figure 45.6). The parents had been told at the visit that the mass was the baby's hand, which highlights the difficulty of identifying facial anomalies via standard two-dimensional ultrasonography (although there is a case report of congenital epulis diagnosed at 26 weeks' gestation).<sup>4</sup> The growing popularity of three-dimensional fetal ultrasonography through concierge prenatal imaging services may allow detection of more facial anomalies antenatally in nonobstetric settings. However, no system currently exists to ensure proper interpretation of such findings and communication of such information to the medical clinicians for further confirmation and subsequent management.



**Figure 45.6.** Prenatal three-dimensional ultrasonography at 32 weeks' gestation shows an irregular mass in the region of the left side of the mouth.

*Peter J. Koltai, Wen-Chun Jimmy Lan, MD, MS, Dylan K. Chan, MD, PhD, Stephen R. Hoff, MD, Stanford University School of Medicine, Palo Alto, CA*

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## Black Lesion on the Tongue

### The Case

A term female newborn presents with a solitary, well-circumscribed black lesion on the dorsum of the tongue that measures  $0.5 \times 0.5$  cm (Figure 46.1).



**Figure 46.1.**

### ***Prenatal history***

- 20-year-old, gravida 3 para 0 (1 preterm birth, 1 loss before 20 weeks, and 1 living child), Hispanic mother
- All prenatal laboratory results are within normal limits
- Prenatal ultrasonography revealed no structural abnormalities
- Denies any exposure to drugs, alcohol, or toxins
- Uneventful prenatal course

### ***Birth History***

- Female infant born via extramural normal spontaneous vaginal delivery by emergency medical services (EMS) personnel at 39 weeks of gestation with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively
- Birthweight of 2,925 g
- Infant brought to the hospital via EMS with a presenting temperature of 97.1°F (36.2°C)
- Admitted to the neonatal intensive care unit in view of extramural delivery and hypothermia

### ***Case Progression***

#### ***Vital Signs***

Temperature: 98.4°F (36.9°C)

Respiratory rate: 58 breaths/min

Heart rate: 131 beats/min

Blood pressure: 77/45 mm Hg

Oxygen saturation: 99% on room air

Birthweight: 2,925 g (25th percentile)

Length: 50 cm (50th percentile)

Head circumference: 33.5 cm (25th percentile)

#### ***Physical Examination***

Head: Normocephalic, anterior fontanelle soft and flat, left parietal cephalhematoma 3 × 3 cm, normal hair pattern

Pupils equal and reactive to light, red reflex present, normal sclera, normal nose and ears

Oral cavity: A well-circumscribed black lesion on the right side dorsum of the tongue measuring  $0.5 \times 0.5$  cm, flat, no epulis, no ranula, no lesions on palate, no cleft lip or palate

Lungs: Clear, good bilateral air entry

Heart: Normal S1, S2; regular rate and rhythm; no murmurs or gallops

Abdomen: Soft, nondistended, no hepatosplenomegaly

Genitourinary: Normal term female genitalia, patent anus, no sacral dimple or tuft

Skeletal: Spine appears normal; symmetric appendages

Neurologic: Alert, active, moving all extremities, normal tone and reflexes

Skin: No rashes, lesions, petechiae, or jaundice

### ***Family History***

- No history of malignant tumors
- No history of skin lesions

### ***Hospital Course***

- Infant initially in an isolette until stabilization of body temperature, then placed in an open crib
- Tolerating full feeds

### ***Laboratory Studies***

- Complete blood cell count: White blood cells, 13,500/mcL ( $13.5 \times 10^9/L$ ); hemoglobin, 15.5 g/dl (155 g/L); hematocrit, 45.9% (0.459); platelets,  $325 \times 10^3/mcL$  ( $325 \times 10^9/L$ ) with normal differential
- Blood culture: No growth
- Urine toxicology result: Negative
- Newborn screening result: Negative

### ***Differential Diagnosis***

#### ***Solitary, Well-Circumscribed Black Lesion on the Dorsum of the Tongue***

Physiologic condition in pigmented races

Hemangiomas

Nevi

Posttraumatic lesion



## Melanotic macule

Pigmented lesions associated with endocrine disorders or different syndromes (Peutz-Jeghers, neurofibromatosis, Addison disease)

*Take a moment to consider the diagnosis in this infant.*

## Actual Diagnosis

Congenital lingual melanotic macule is a clinically distinct entity. It has been observed as a solitary or multiple well-circumscribed, brown lesion(s) on the dorsal surface of the tongue at birth that grows proportionately to the tongue.

## The Experts

The cause of congenital lingual melanotic macule is unclear. It is possible that the congenital lesions may represent a hematoma of melanocytes with localized functional change in melanin production. There are sporadic reports of acquired oral melanotic macules appearing after trauma, irradiation, or medication. Various hypotheses for localized increased melanin production in these cases have included physiologic genetic variations or viral and immunologic factors, but none has been conclusive.

Oral hyperpigmentation is a common event in older individuals but is exceptional in neonates. When hyperpigmentation is present, the clinical diagnosis is not always immediately apparent. Congenital lingual melanotic macules are a rare entity, of which there are only 7 well-documented cases reported in the literature. All cases were present at birth and had grown proportionately since, with sizes ranging from 0.3 to 3 cm.

Various terms are used for oral melanotic macules of the mucosa and skin, such as *ephelides*, *melanosis*, *lentigo*, *labial lentigo*, *melanotic macule*, and *oral melanocytosis*. Current terms for lesions with characteristic features of oral and lingual melanotic macules have been standardized by Weathers et al in 1976 and Page et al in 1977.

Clinical diagnosis of congenital lingual melanotic macule should be considered when the following criteria apply: solitary or multiple melanotic lesions on the tongue, lesion present at birth with subsequent proportional growth, and a negative family history of systemic conditions associated with mucosal pigmentation. The size ranges from 0.3 to 3 cm.

The consistent histologic features include increased basal pigmentation with varying degrees of overlying hyperkeratosis. Melanocytic hyperplasia and mild pigment incontinence are minimal. Mitoses or cytologic atypia were not found.

Primary malignant melanoma of the oral cavity accounts for approximately 0.2% to 8% of all melanomas and shows a distinct predilection for the maxillary alveolar ridge and palate, whereas the tongue represents a rather unusual site. It is most commonly seen in the 40- to 70-year age group, and there is just 1 histologically documented transformation of benign oral melanosis into malignant melanoma in an adult patient.

## Conclusion

Congenital melanotic macule shares the benign histologic features of other oral melanotic macules, and a biopsy is recommended to ascertain this. Although oral melanotic macules are considered benign, careful follow-up is recommended because of the histologically documented transformation of benign oral melanosis into malignant melanoma in an adult.

*Radhika Narang, MD, Kavya Puranik, MD, Mary Marron-Corwin, MD, Harlem Hospital Center, New York, NY, and Columbia University, New York, NY*

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*Part 13*

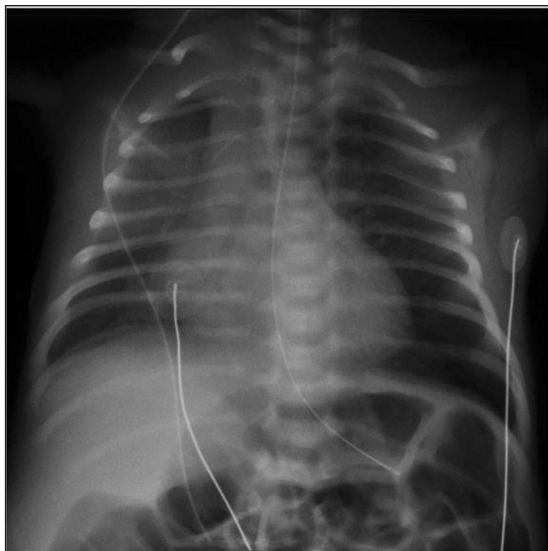
# **Pulmonology**

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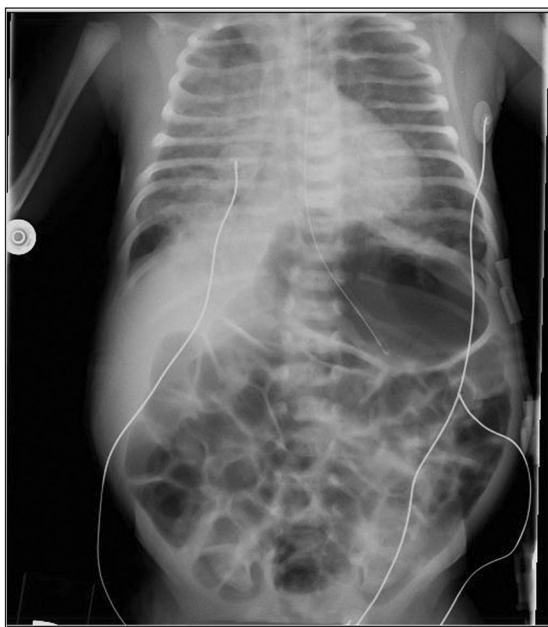
## **Late Preterm Baby With Recurrent Respiratory Distress**

### **Presentation**

A 34-week preterm baby (triplet C) is born of a triplet gestation to a 29-year-old gravida 2 para 3 mother after conception by in vitro fertilization. The mother is on thyroxine hormone for hypothyroidism and glyburide for diabetes mellitus. Delivery is by cesarean delivery at 34 weeks' gestation due to progressively worsening maternal hypertension and a low biophysical profile of triplet B. Delivery room stabilization includes positive pressure ventilation, intubation, and surfactant administration. Apgar scores are 6 at 1 minute and 8 at 5 minutes. Birthweight is 2,380 g (50th–75th percentile), length is 46 cm (50th–75th percentile), and head circumference is 33.4 cm (75th–90th percentile). He is extubated to continuous positive airway pressure in a few hours, and respiratory support is weaned to humidified high flow through nasal cannula. Feedings are commenced when he is 4 days old and gradually advanced. He vomits and has desaturation with worsening respiratory distress and requires increased respiratory support with each attempt to increase feeds. Radiologic evaluation reveals progressively worsening parenchymal haziness (Figures 47.1 and 47.2). After feeds are stopped, his respiratory status improves, and he is weaned down to baseline respiratory support. Radiologic evaluation leads to suspicion of the diagnosis followed by a confirmatory test.



**Figure 47.1.** Chest radiograph with clear lung fields.



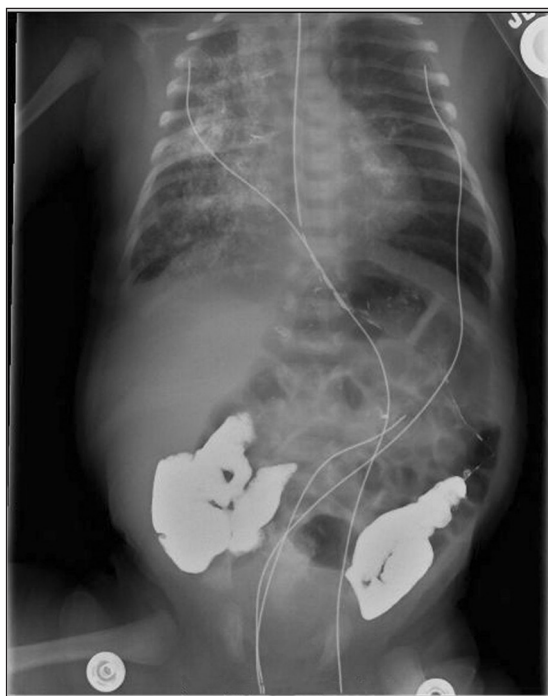
**Figure 47.2.** Chest and abdominal radiograph showing bilateral parenchymal haziness (right greater than left side), large stomach bowel and areas of mildly distended bowel loops.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

### Diagnosis

An upper gastrointestinal contrast study reveals contrast in the tracheobronchial tree, suggestive of either aspiration or a tracheoesophageal fistula (TEF) (Figure 47.3). Rigid bronchoscopy and esophagoscopy are deferred to allow for somatic growth while the child is enterally fed through a nasojejunal tube. Subsequent rigid bronchoscopy reveals a normal carina and right and left mainstem bronchi. Inspection of the anterior aspect of the trachea shows no abnormalities. Inspection of the posterior trachea reveals a fistulous opening approximately 2.7 cm proximal to the carina that increases in size with positive pressure. A 2F Fogarty catheter is introduced through the working port of the rigid bronchoscope and passes easily through the fistulous opening. Simultaneous flexible esophagoscopy with a neonatal esophagoscope demonstrates a normal-appearing esophagus, an indwelling orogastric tube, and the presence of the Fogarty catheter within the esophageal lumen, confirming the H-type TEF. Echocardiogram shows a small, septum secundum atrial septal defect. Skeletal survey and head, spinal, and renal ultrasounds are normal.



**Figure 47.3.** Babygram obtained after an upper gastrointestinal contrast study that shows contrast in the tracheobronchial tree, suggestive of either aspiration or a tracheoesophageal fistula.





**Figure 47.4.** Posterior trachea with a fistulous opening that increases in size with positive pressure. (Reproduced with permission of Akshaya Vachharajani, MD. Copyright 2012.) View the video at <http://neoreviews.aappublications.org/content/15/5/e199>.

## ***The Condition***

Tracheoesophageal fistula is an abnormal communication between the trachea and the esophagus. It was classified by Gross into the following types:

Type A: presence of a proximal and distal esophageal bud with a missing midsegment. No communication with the trachea.

Type B: proximal esophageal termination on the lower trachea with distal esophageal bud.

Type C: proximal esophageal atresia (esophagus ends in a blind loop superior to the sternal angle) with a distal esophagus arising from the lower trachea or carina. This is the most common variety and accounts for 90% of all cases of TEF.

Type D: proximal esophageal termination on the lower trachea or carina with distal esophagus arising from the carina.

Type E: a variant of type D; if the two segments of esophagus communicate, this is sometimes termed an H-type fistula because of its resemblance to the letter H.

The H type is the least common variant of TEF and accounts for only approximately 4% to 5% of total cases. The commonest level at which it occurs is the second thoracic vertebra. It has the lowest incidence of associated congenital anomalies and the best prognosis among all varieties of TEF. Polyhydramnios is rare, and intra-uterine growth is usually normal. Clinically, it is characterized by the classic triad of recurrent episodes of choking and coughing with feeding, lower respiratory tract infections, and abdominal distension as air passes through the fistula into the stomach.

In any infant presenting with these symptoms, an H-type TEF should be suspected. Bronchoscopy with or without esophagoscopy is the diagnostic gold standard. Surgical treatment consists of ligation and repair of the fistula, usually through a cervical approach, although a thoracoscopic approach or thoracotomy may be required depending on the level of the fistula.

### **Case Progression**

The fistula was repaired through a right-sided cervical approach. The patient developed stridor, with increased work of breathing in the immediate postoperative period that steadily improved over the next few days. Oral feedings were commenced on postoperative day 4, well tolerated, and gradually increased to goal. Flexible nasolaryngoscopy was performed 2 weeks after the surgery for persistent stridor, which showed right vocal cord paresis. The stridor continued to improve, and he was discharged home. Follow-up nasolaryngoscopy showed return of right vocal cord function.

### **Lessons for the Clinician**

Recurrent episodes of choking, coughing, and respiratory distress with feeds can be caused by an H-type TEF. It has the best prognosis among all types of TEF.

*Parul G. Zaveri, MD, Adam M. Vogel, MD, Akshaya J. Vachharajani, MD, Washington University School of Medicine, St Louis Children's Hospital, St Louis, MO*

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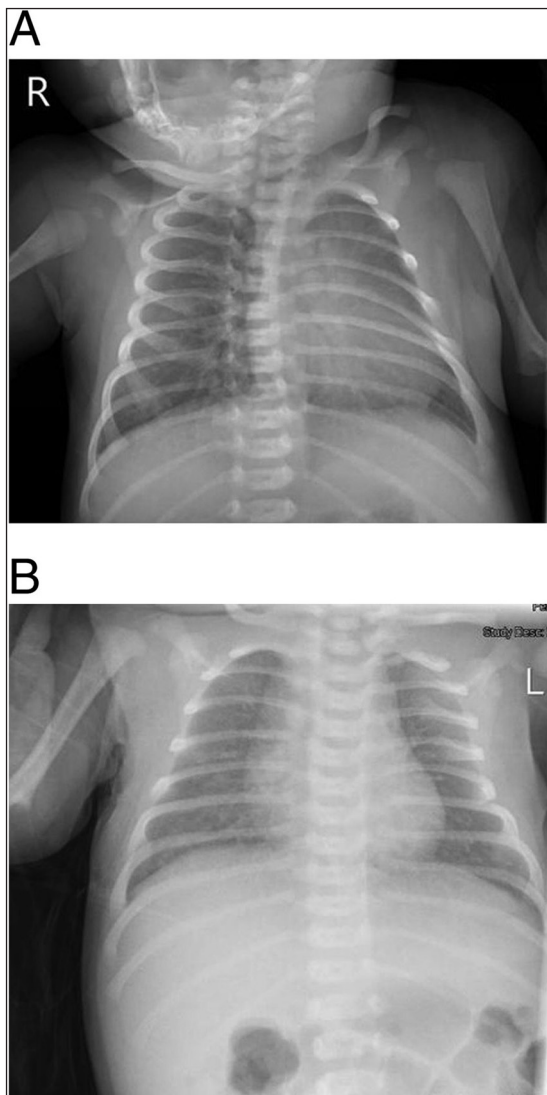
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## Persistent Tachypnea in a Newborn

### Presentation

At 2 days of age, a term female newborn is evaluated for tachypnea. She was born at 40 weeks' gestation, with birthweight 4.6 kg, to a 34-year-old G2P2 woman via normal spontaneous vaginal delivery. Maternal history is pertinent for well-controlled gestational diabetes mellitus and hypothyroidism treated with levothyroxine. Prenatal laboratories are significant for group B *Streptococcus* positivity for which the mother was adequately treated. All other prenatal laboratories are unremarkable. The delivery was complicated by a nuchal cord and apnea requiring positive pressure ventilation for 10 seconds. Apgar scores were 6 at 1 minute and 9 at 5 minutes. A review of her vital signs from the newborn nursery reveal the following: heart rate, 128 beats per minute; respiratory rate, 52 breaths per minute; and oxygen saturation, 89% in room air that had improved without supplemental oxygen.

Her respiratory rate is 82 breaths per minute, and pre- and postductal oxygen saturations are 97% in room air. On physical examination, she is consistently tachypneic, as noted by multiple caregivers, with minimal subcostal retractions but without grunting or flaring. The remainder of her examination is within normal limits. Basic metabolic panel, capillary blood gas, and complete blood count are all normal. A chest radiograph is read as unremarkable (Figure 48.1A). Blood cultures are drawn, but given a low risk for sepsis, antibiotics are not started. A cardiologist is consulted for sustained tachypnea and a new grade I/VI systolic murmur in the left lower sternal border. An echocardiogram reveals two small mid-muscular ventricular septal defects, a small patent foramen ovale, and a small patent ductus arteriosus, none of which is thought to be hemodynamically significant. A repeat chest radiograph reveals mild pulmonary venous congestion (Figure 48.1B). A pulmonologist is consulted and recommends a high-resolution computed tomography (CT) scan of the chest. The CT scan demonstrates increased interstitial markings in the right lung without consolidation (Figure 48.2). Given the suggestive CT findings, the consultant recommends a definitive procedure that reveals the diagnosis.



**Figure 48.1.** A. Chest radiograph on age 2 days. No pulmonary consolidation, pleural effusion, pneumothorax, or vascular congestion is evident. B. Chest radiograph on age 4 days. Mild pulmonary venous congestion, which may be related to the patient's history of ventricular septal defect versus a poor inspiratory effort. This is new when compared with the previous examination.



**Figure 48.2.** High-resolution CT scan of the chest on age 6 days. Increased interstitial markings in the right lung, especially in the periphery without confluent infiltrates. No adenopathy or pleural fluid noted.

### Differential Diagnosis

Interstitial lung diseases of the infant and child can be grouped into five main categories: diffuse developmental disorders, surfactant dysfunction disorders, growth abnormalities, neuroendocrine cell hyperplasia of infancy, and pulmonary interstitial glycogenosis (PIG; Table 48.1).<sup>1</sup>

**Table 48.1. Differential Diagnosis of Childhood Interstitial Lung Disease**

Diffuse developmental disorders
Alveolar capillary dysgenesis
Congenital alveolar dysplasia
Alveolar capillary dysplasia associated with misalignment of pulmonary veins
Growth abnormalities
Pulmonary hypoplasia
Chronic lung disease of prematurity
Trisomy 21
Congenital heart disease
Surfactant dysfunction disorders
Surfactant protein (SP) B and C deficiency
ATP-binding cassette A3 (ABCA3) deficiency
Thyroid transcription factor mutations
Neuroendocrine cell hyperplasia of infancy
Pulmonary interstitial glycogenosis (PIG)

Diffuse developmental disorders are severe (and almost universally fatal) disorders of alveolar development that include acinar/alveolar dysgenesis, congenital alveolar dysplasia, and alveolar capillary dysplasia associated with misalignment of pulmonary veins. The latter is the most common of these but is still rare.

Growth abnormalities include pulmonary hypoplasia, chronic lung disease of prematurity, congenital heart disease–associated abnormalities, and trisomy 21–associated abnormalities. These conditions lead to alveolar simplification of different degrees, with varying rates of mortality (up to 34%).

The presentation of surfactant dysfunction or metabolism disorders (ABCA3 deficiency, SP B and C deficiency) can be pronounced with respiratory failure at birth or subtler later in childhood with tachypnea and hypoxemia, and prognosis is also variable.

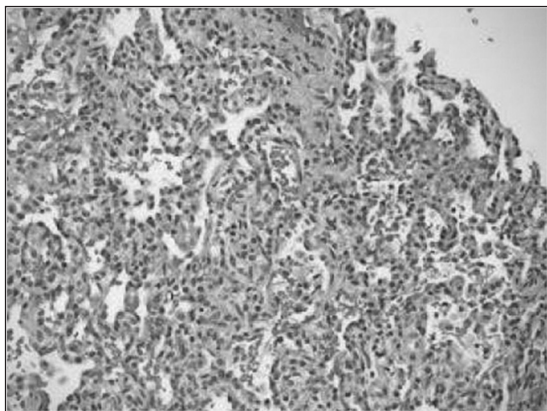
Neuroendocrine cell hyperplasia of infancy presents during the first year after birth with respiratory distress and hypoxemia; CT scans will typically reveal ground-glass opacities in the right middle lobe and left lingula, as well as lower-lobe air trapping. Histology demonstrates hyperplasia of neuroendocrine cells in alveolar ducts and distal bronchioles.

Pulmonary interstitial glycogenosis is characterized by a widened interstitium secondary to mesenchymal cells filled with glycogen that interferes with appropriate gas exchange. It usually presents during the neonatal period with tachypnea and/or hypoxemia.

*Take a moment to consider the diagnosis in this infant.*

## **The Condition**

The patient is taken to the operating room, and a right lower lobe wedge biopsy is performed via video-assisted thoracoscopic surgery (VATS), revealing a diagnosis of PIG (Figure 48.3). It should be noted that, with more widespread use of VATS, obtaining lung tissue is a safe and well-tolerated procedure, leaving patients with only a small scar after the chest drain is removed.



**Figure 48.3.** High-power view of wedge biopsy revealing PIG (hematoxylin & eosin stain). Of note, subsequent chromogranin QL staining demonstrated no evidence of neuroendocrine cell hyperplasia.

Pulmonary interstitial glycogenosis was first described in 2002 by Canakis et al.<sup>2</sup> Of the 7 patients described, 5 required mechanical ventilation with 4 of these being preterm. Although generally diagnosed in the neonatal period, PIG has been diagnosed later in infancy, with 1 center reporting positive biopsies in infants up to 8 months of age.<sup>1</sup>

Tissue biopsy is required to make the diagnosis. Periodic acid-Schiff stain demonstrates glycogen-filled mesenchymal cells.<sup>1</sup> Electron microscopy is helpful and often necessary to confirm a diagnosis of PIG. Because the interstitium is effectively widened by intracellular glycogen, gas exchange is impaired and neonates typically present with tachypnea and hypoxemia exaggerated compared with the clinical circumstances. In the case of our patient, she presented with tachypnea and mild, transient hypoxemia, suggesting a less severe form of PIG than other case reports.

## Management

There are no established guidelines for the management of PIG, and controlled trials are lacking. In nearly all cases reported, treatment has been either via pulse corticosteroids or a simple “watch and wait” approach. Because PIG is thought to be due to delayed maturation of interstitial cells rather than true interstitial inflammation, it is possible that corticosteroids may help to accelerate the maturation process.<sup>1</sup> Most infants with PIG do well and show resolution of tachypnea and associated hypoxemia.

In almost all reported cases,<sup>2,3,4</sup> patients demonstrated improvement either with or without the use of systemic corticosteroids. In the case series by Canakis et al.,<sup>2</sup> 5 of 7 patients were treated with corticosteroids, 3 of whom were followed up to 6 years. At follow-up, 2 of the 3 patients reported using bronchodilators and inhaled corticosteroids during episodes of respiratory illness, but between episodes all 3 were asymptomatic. In another case of PIG, lung biopsies were done at 10 days and



49 days, before and after treatment with corticosteroids; after corticosteroids, the mesenchymal cells had greatly decreased in number with many cells demonstrating apoptotic markers and decreased markers of cell proliferation.<sup>5</sup>

For our patient, the decision was made not to use corticosteroids because her tachypnea was resolving and she had no oxygen requirement during most of her hospitalization and upon discharge. She is currently almost 12 months old, and at follow-up, we are happy to report she remains asymptomatic.

### **Lessons for the Clinician**

Tachypnea should be investigated thoroughly in the absence of a satisfactory explanation, including complete radiologic examinations.

Video-assisted thoracoscopic surgery can be safely and easily performed even in newborns.

New categories of interstitial lung disease have recently been described in pediatrics; several of these conditions may present in the newborn period and may require extensive evaluation.

Colin L. Robinson, MD, MPH, Peter Chau, MD, Stacey Logan, MD, Christopher Harris, MD, University of California-Los Angeles, Los Angeles, CA, and Cedars-Sinai Medical Center, Los Angeles, CA

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### **COMMENTARY BY DR DARA BRODSKY, MD, BETH ISRAEL DEACONESS MEDICAL CENTER**

An update on the classification system, evaluation, and prognosis for interstitial lung disease of infancy can be found in Thacker PG, Vargas SO, Fishman MP, Casey AM, Lee EY. Current update on interstitial lung disease of infancy: new classification system, diagnostic evaluation, imaging algorithms, imaging findings, and prognosis. *Radiol Clin North Am*. 2016;54(6):1065–1076

# **Persistent Hypoxemia and Pulmonary Hypertension in a 3-Day-Old Infant**

## **The Case**

### ***History of Present Illness***

A 3-day-old ex-term Caucasian female with persistent hypoxemia and pulmonary hypertension presents from an outside community neonatal intensive care unit (NICU) for possible extracorporeal membrane oxygenation (ECMO) therapy.

### ***Prenatal History***

The patient was born to a 27-year-old gravida 4 mother who received prenatal care from early in the first trimester. An initial prenatal ultrasound showed a two-vessel cord and bilateral hydronephrosis; a higher-level ultrasound did not show any evidence of congenital heart disease.

### ***Family History***

There is no history of consanguinity in the family. The patient's aunt has congenital heart disease, and the brother has hydrocephalus and hydronephrosis of unknown etiology.

### ***Birth History***

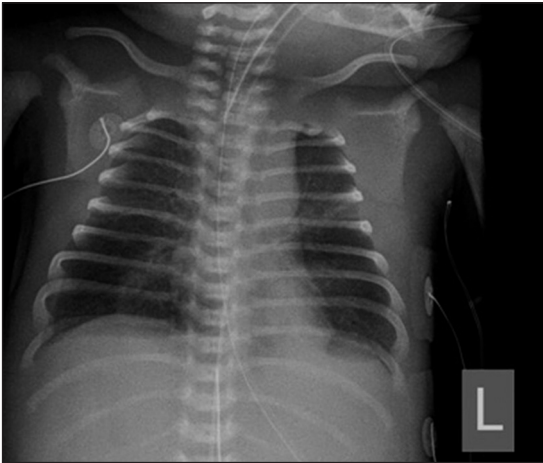
She weighed 3,500 grams and was born at an estimated 39 weeks gestation via repeat cesarean section with rupture of membranes and clear amniotic fluid at the time of delivery.

She received routine care at delivery and transitioned well with Apgars of 8 and 9 at 1 and 5 minutes, respectively.

## Case Progression

### Initial Presentation

She was initially noted to be dusky in the newborn nursery 4 hours after delivery and was transferred emergently to the NICU for evaluation. An initial chest radiograph showed a small cardiac silhouette with clear lung fields; the initial complete blood count did not have findings suggestive of infection (Figure 49.1).



**Figure 49.1.** Chest radiograph in a term intubated newborn with a small cardiac silhouette and clear lung fields.

Congenital heart disease was suspected after a hyperoxia test showed a preductal  $\text{PaO}_2$  of 71 mm Hg. A prostaglandin  $\text{E}_1$  infusion was started, and she was transferred to a higher level of care for further evaluation.

At an outside Level III NICU, her hypoxemia worsened, and she was eventually transitioned to high-frequency oscillatory ventilation with a peak mean airway pressure of 17 cm  $\text{H}_2\text{O}$  and 100% oxygen. A postnatal echocardiogram showed no structural abnormalities. Persistent pulmonary hypertension (PPHN) was suspected, and dopamine and epinephrine were initiated for inotropic support. Because of persistent hypoxemia, inhaled nitric oxide (iNO) was initiated with a transient improvement in  $\text{PaO}_2$  before returning to the 40-50 mm Hg range. The calculated oxygenation index was 38, and transfer to a regional ECMO center was undertaken.

### Physical Exam on Arrival to the ECMO Center

The patient was intubated and sedated. No dysmorphic features were noted. The examination revealed no other abnormalities.

***ECMO Course***

The patient was placed on veno-arterial ECMO soon after arrival. After 5 days of support, she was weaned to minimal flows with the addition of iNO and 50% oxygen. An echocardiogram performed at that time showed septal bowing, right ventricular hypertension, and tricuspid regurgitation suggestive of suprasystemic pulmonary pressures. Two pulmonary veins were seen draining into the left atrium. There were no structural abnormalities noted. Sildenafil and epoprostenol were subsequently added.

Eleven subsequent echocardiograms were performed over the following days to evaluate her pulmonary hypertension and showed no improvement. She was subsequently taken for cardiac catheterization.

***Differential Diagnosis of Pulmonary Hypertension in a Newborn******Functional Vasoconstriction***

Perinatal asphyxia

Meconium aspiration

Sepsis

Pneumonia

Respiratory distress syndrome

Air leak

Total anomalous pulmonary venous return

***Functional Obstruction***

Polycythemia

Hyperfibrinogenemia

***Maldevelopment of the Pulmonary Vasculature***

Placental insufficiency

Prenatal closure of the patent ductus arteriosus (e.g., maternal nonsteroidal anti-inflammatory drug administration)

***Underdevelopment of the Pulmonary Vasculature***

Congenital diaphragmatic hernia

Pulmonary hypoplasia

Alveolar capillary dysplasia

*Take a moment to consider the diagnosis in this infant.*

## **Actual Diagnosis**

The actual diagnosis appeared to be alveolar capillary dysplasia.

## **Cardiac Catheterization**

Cardiac catheterization revealed a discrete juxtaductal coarctation of the aorta; no other structural abnormalities were seen. Pulmonary veins were seen returning to the left atrium without evidence of obstruction.

The pulmonary arterial pressure was noted to be suprasystemic with markedly decreased pulmonary blood flow. Distal pulmonary artery branches were noted to be sparse and “pruned” in appearance.

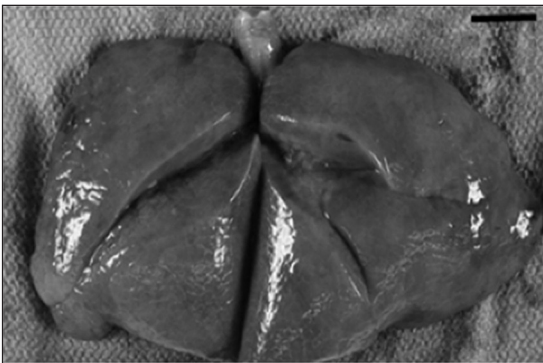
A right pulmonary arterial wedge angiogram was performed, and a diminished alveolar capillary “blush” phase was noted. These findings are all consistent with a diagnosis of alveolar capillary dysplasia (ACD).

## **Post Catheterization**

The patient’s family was informed of the findings, the strong suspicion of ACD, as well as its uniformly fatal course. A transition to comfort care was made, and she expired shortly after decannulation and extubation. Consent for postmortem examination was granted by the patient’s family.

## **Postmortem Findings**

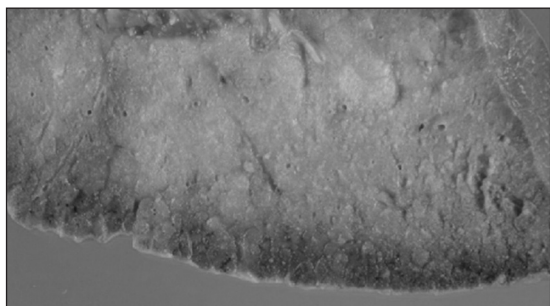
Initial examination of the lungs (Figure 49.2) showed heavy lungs, with typical lobulation (95 g combined weight, with 64 g  $\pm$  27 g expected).



**Figure 49.2.** Postmortem lung of a newborn with lobulation and greater size than normal.

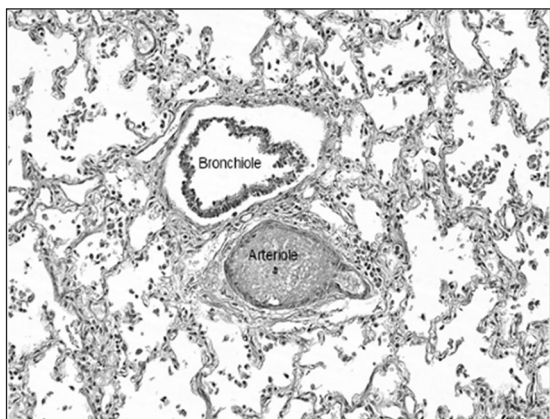
Gross distention of distal lymphatic spaces was apparent upon gross examination of the lungs. Microscopic examination confirmed dilation of both proximal and distal lymphatic spaces.

In a normal lung, bronchioles and pulmonary arterioles follow the same course, and pulmonary venules are located separately, as depicted in an age-matched control lung from autopsy (Figure 49.3).



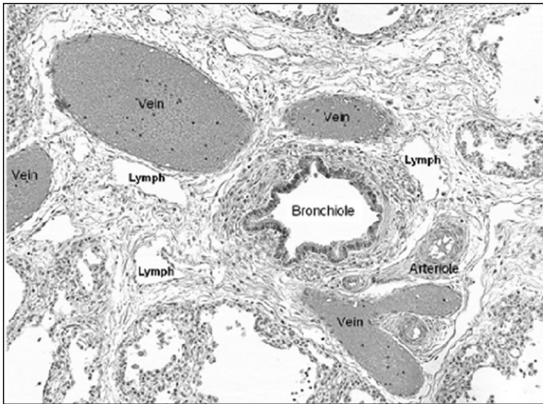
**Figure 49.3.** Normal lung tissue.

In this patient, microscopic examination (Figure 49.4) further revealed malposition of pulmonary vein branches, with distended venules localized adjacent to pulmonary arterioles. In addition to prominent venous and lymphatic dilation, marked enhancement of muscle with the walls of small- and medium-sized intra-acinar pulmonary arterioles was apparent. These dysplastic features and abnormal architecture of pulmonary acini were apparent in all microscopic fields examined.



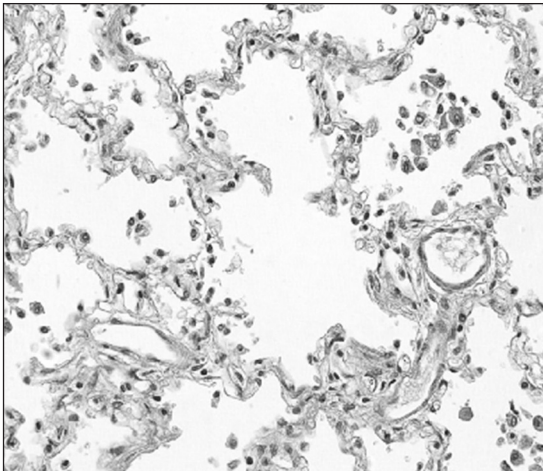
**Figure 49.4.** Microscopic lung examination showing abnormal lung architecture.

In a normal lung, as depicted in an age-matched control lung from autopsy (Figure 49.5), alveolar capillaries are adjacent to air spaces, and the alveolar-capillary membrane interface is thin. This anatomic configuration facilitates appropriate air exchange in each of the 150 million alveoli within the normal lung, with 70% of the normal alveolar surface area covered by a capillary network.



**Figure 49.5.** Normal lung tissue showing alveolar capillaries adjacent to air spaces and a thin alveolar-capillary membrane interface.

In this patient with ACD (Figure 49.6), a paucity of capillaries adjacent to the alveolar epithelium is apparent, as is a diffuse widening of the interstitial spaces and consequential thickening of alveolar walls. This removal of alveolar capillaries from the alveolar air interface impairs normal gas exchange, resulting in pulmonary hypertension.



**Figure 49.6.** A diagnosis of alveolar capillary dysplasia is evident in this lung examination because of a paucity of capillaries adjacent to alveolar epithelium, wide interstitial spaces, and thickened alveolar walls.

Additional visceral malformations were present, including intestinal malrotation with a left-sided cecum and appendix, as well as congenital absence of the gallbladder. Bilateral hydronephrosis was present with dilated proximal ureters at the site of entry into the renal pelvis. Multiple bilateral follicular ovarian cysts were detectable just below the lower pole of the kidney.



## The Experts

This constellation of clinical and postmortem findings is diagnostic of ACD. First reported by Janney et al in 1981, ACD has been well described in the literature as a cause of PPHN.<sup>1</sup> Alveolar capillary dysplasia is a disorder of pulmonary vascular development in which there are characteristic histologic features, including a paucity of capillaries adjacent the pulmonary epithelium, anomalously placed pulmonary veins, medial muscularization of pulmonary arterioles, and small immature alveoli.<sup>2</sup> Involvement is typically diffuse and widespread, though in 14% of cases there is patchy involvement that leads to presentation at 2–6 weeks.<sup>3</sup>

Clinically, infants with this disorder have fulminant, severe pulmonary hypertension secondary to their marked reduction in intra-acinar capillaries.<sup>4</sup> They typically transition well with normal Apgar scores, and then decompensate, presenting with respiratory distress.<sup>2</sup> Respiratory support escalates quickly, and in some cases there is a *transient* response to iNO.<sup>5</sup> The pulmonary hypertension, however, is unremitting.

Studies of families with ACD suggest that there may be a genetic basis. Pedigrees of families afflicted with ACD show that 12% of families have had a child with pulmonary hypertension, and many have known sibling pairs with a history of ACD.<sup>6</sup> A number of anomalies have been observed in ACD. Cardiac anomalies include coarctation, cor triatriatum, atrial septal defect, and atrioventricular canal. Gastrointestinal abnormalities include malrotation, heterotaxy, imperforate anus, Hirschsprung disease and congenital diaphragmatic hernia. Hydronephrosis and ureteropelvic junction obstruction can also be seen, as can phocomelia.<sup>6</sup>

A number of modalities have been used to confirm the diagnosis of ACD. Open lung biopsy has been tried, but this is often risky in an anticoagulated patient on ECMO or an infant with patchy involvement. Cardiac catheterization can show characteristic findings. “Pruning” occurs because of the sparse number of distal pulmonary arteries as well as the marked reduction in the number of intra-acinar capillaries and in subsequent blood flow. The absent or diminished alveolar capillary blush phase describes the absence of dark contrast in the segment of the lung in which a pulmonary wedge angiogram is being performed. In ACD, significant pulmonary hypertension forces blood entering an acinus to drain through a misaligned pulmonary vein instead of the few intra-acinar capillaries, thus eliminating or diminishing the “blush” that is normally seen.<sup>4</sup>

Presently, there are no known means of treating patients with ACD. Establishing the diagnosis prior to postmortem examination is important, as confirming the diagnosis beforehand can lead to decreased suffering for the patient and family as well as better allocation of expensive resources such as ECMO.<sup>4</sup>

Anand Rajani, Monique T. Barakat, Charay Jennings, Stanford University School of Medicine



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### COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER

An update of the classification system, evaluation, and prognosis for interstitial lung disease of infancy can be found in Thacker PG, Vargas SO, Fishman MP, Casey, AM, Lee EY. Current update on interstitial lung disease of infancy: new classification system, diagnostic evaluation, imaging algorithms, imaging findings, and prognosis. *Radiol Clin North Am*. 2016;54(6):1065–1076

## **Respiratory Compromise and Abdominal Wall Crepitus in a 3-Week-Old Infant**

### **The Case**

A 3-week-old female infant, who had been born at term with pneumonia, presents with sudden respiratory compromise and abdominal wall crepitus. Pertinent points in the history include:

Born to a 24-year-old G2P1 mother whose prenatal course was complicated by recurrent urinary tract infections. Prenatal laboratory results: rapid plasma reagin test, nonreactive; group B *Streptococcus*, negative; HIV, negative; rubella, immune; herpes simplex virus (HSV), unknown.

Delivered by normal spontaneous vaginal delivery without complication; Apgar scores of 9 at 1 minute and 9 at 5 minutes.

Developed progressive respiratory distress, with pneumonia diagnosed when 3 days old.

Required conventional mechanical ventilation for 9 days, followed by weaning to nasal cannula oxygen; chest radiograph at this time was significant for a left lower lobe pneumatocele.

At 21 days of age, developed sudden respiratory compromise requiring reintubation and high-frequency oscillation; physical examination at this time revealed abdominal wall crepitus (Figure 50.1).



**Figure 50.1.** Three-week-old term infant who is intubated and critically ill.

### ***Case Progression***

Respiratory collapse ensued.

Mean arterial pressure decreased to 25 mm Hg.

Difficulty oxygenating with high-frequency oscillating ventilator.

Initial radiograph (Figure 50.2) demonstrated tension pneumothorax on the left, and a persistent cystic lucency in the left lower lobe.



**Figure 50.2.** Anteroposterior chest radiograph showing left-sided pneumothorax with midline shift.

Abdomen became distended; physical examination revealed crepitus over the abdominal wall.

Subsequent radiographs (Figures 50.3–50.6) obtained to evaluate chest tube placement showed massive subcutaneous air.

Bronchoalveolar lavage (BAL) was performed to investigate infectious causes of the cystic mass.

Laboratory investigation was positive for infection.

BAL culture was positive for HSV type 2.

Blood, urine, and cerebrospinal fluid cultures were negative.

Cerebrospinal fluid HSV polymerase chain reaction was negative.

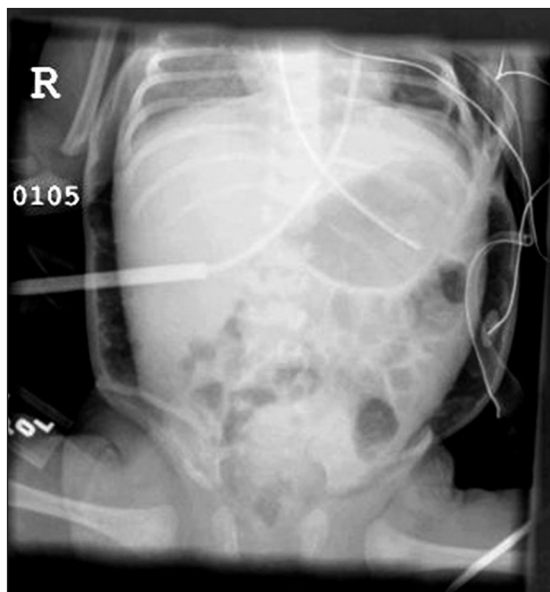
Rectal, conjunctival, and nasopharyngeal direct fluorescent antibody examinations for respiratory viruses were negative.

No skin lesions.

Transaminases were normal.



**Figures 50.3.** Subsequent radiographs.



**Figures 50.4.** Subsequent radiographs.



**Figures 50.5.** Subsequent radiographs.



**Figures 50.6.** Subsequent radiographs.

## ***Management***

Due to the persistent air leak after chest tube placement and the progressive subcutaneous emphysema, the left lower lobe was removed surgically. The patient recovered well after a 21-day course of acyclovir therapy. The subcutaneous emphysema resolved slowly over the following 2 weeks.

## ***Differential Diagnosis***

### ***Subcutaneous Emphysema***

Bronchopleural fistula (pleurocutaneous fistula)

Infection

Necrotizing fasciitis (production of gas within a tissue)

Trauma (inadvertent introduction of air into a tissue)

- Esophageal rupture
- Ruptured bronchial tube
- Alveolar rupture resulting in pneumothorax

Spontaneous perforation of a hollow viscus

*Take a moment to consider the diagnosis in this infant.*

## **Actual Diagnosis**

### ***Bronchopleural Fistula***

## **Management**

Left lower lobectomy to resolve persistent air leak.

## **The Experts**

Subcutaneous emphysema is defined as the presence of gas within the tissue beneath the skin. It is a rare finding that usually is related to the inadvertent introduction of air into tissues (such as through an air leak from the lung). It also can occur following the production of gas within a tissue by infection such as in gas gangrene.

On physical examination, subcutaneous emphysema presents as a smooth bulging of the skin (Figure 50.1). Palpation produces an unusual crackling sensation as the gas is pushed through the tissue (crepitus).

The evaluation should encompass areas distant from the site of involvement, because free air often spreads throughout the interstitium, following the paths of least resistance. The anatomy of deep fascial planes allows free air to enter the subcutaneous tissue from internal sources.

From the mediastinum, air can extend into the chest wall, neck, and face along several pathways consisting of potential spaces between fascial planes investing the trachea, esophagus, and great vessels. Pneumothorax in the newborn is one of several conditions that are produced by air block. It has been shown experimentally that overdistension of lung, usually due to an obstruction to the exit of air during expiration, causes overdistension of alveoli. Air can leak from the alveoli into the surrounding interstitial tissue and dissect along a perivascular route toward the hilus resulting in interstitial emphysema, with pneumomediastinum occurring when air reaches the mediastinum. Air also may gain access to the pericardium along the perivascular sheaths and cause a pneumopericardium. The increase in mediastinal pressure may be relieved by rupture of the parietal pleura, resulting in a pneumothorax, and much less often by rupture into the subcutaneous tissue or into the space below the diaphragm (pneumoperitoneum).

Treatment of subcutaneous emphysema is directed primarily at the underlying cause. Anecdotal evidence from cases of subcutaneous emphysema caused by pneumomediastinum has shown that inspiration of 100% oxygen helps promote subcutaneous air resorption. In subcutaneous emphysema caused by gas-producing

organisms, such as gas gangrene and necrotizing fasciitis, hyperbaric oxygen appears to have a role in conjunction with surgical debridement and appropriate antibiotic therapy.

Various forms of high-frequency ventilation have been used to treat infants who have pulmonary air leak, and some suggest an advantage of high-frequency ventilation over conventional ventilation. Keszler and associates demonstrated the superiority of high-frequency jet ventilation (HFJV) in the treatment of infants who had pulmonary interstitial emphysema. In a comparison of HFJV with conventional mechanical ventilation, Gonzalez and colleagues documented decreased gas flow through chest tubes among infants who had pneumothoraces and received HFJV.

The mechanism by which HFJV improves the healing of air leaks is not clearly defined, particularly in comparison with the mechanism of conventional mechanical ventilation. One possibility is that the ability of HFJV to oxygenate adequately without the use of high peak inspiratory pressures results in a decreased pressure differential between the ruptured alveoli and the pleural space, decreasing the driving pressure of gas through the site of the leak. Additionally, the size of the site of the air leak likely increases during the peak positive pressure phase of inspiration. The very short absolute inspiratory time and small tidal volume of each HFJV breath may minimize dilation of the site. The decrease in diameter of the air leak then may increase its resistance to gas flow and facilitate its closure.

Alexis Davis, MD and JoDee M. Anderson, MD, Stanford University School of Medicine, Palo Alto, CA

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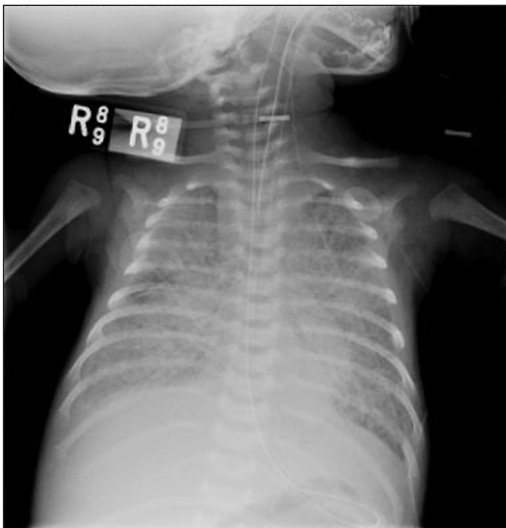


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## Respiratory Distress and Shock at 1 Month of Age

### Presentation

A female infant, born at 36 weeks to a 25-year-old G2P2 mother by normal spontaneous vaginal delivery after an uncomplicated pregnancy, presents with respiratory distress and shock at 1 month of age. She has had 2 days of increased work of breathing with tachypnea and tracheal tugging; 2 weeks of cough, rhinorrhea, and nasal congestion; and currently an episode of cyanosis lasting 2 minutes. Weight gain has been appropriate since birth. On physical examination, rectal temperature is 34°C, heart rate is 126 beats per minute, blood pressure is 58/31 mm Hg, and oxygen saturation is 40% in room air. The patient has prolonged capillary refill indicative of poor peripheral perfusion, coarse breath sounds with rhonchi bilaterally, and hepatosplenomegaly. A chest radiograph shows diffuse, coarse, bilateral interstitial opacities with lucency over the right middle lobe (Figure 51.1).



**Figure 51.1.** Chest radiograph demonstrating bilateral, diffuse, coarse interstitial markings with subsegmental left lower lobe opacity, right midlobe lucency, and small right-sided pleural effusion.

Initial laboratory studies include an arterial blood gas with pH of 7.03, a  $\text{PCO}_2$  of 70 mm Hg, calculated bicarbonate of 18 mEq/L, and a base excess of  $-13$ ; the patient's serum lactate level was 6.7 mmol/L. The white blood cell count is  $25.6 \times 10^3/\text{mcL}$  ( $25.6 \times 10^9/\text{L}$ ) with 41% neutrophils and 38% band forms. The C-reactive protein level is 107 mg/L. The serum total bilirubin is 1.3 mg/dL, alanine aminotransferase is 22 U/L, and aspartate aminotransferase is 88 U/L. Her prothrombin time is 31.9 seconds (international normalized ratio: 3.1), and activated partial thromboplastin time is 51.9 seconds. The cerebrospinal fluid cell count (CSF) cell count, differential, protein, and glucose are normal. Samples of blood, urine, CSF, and endotracheal tube aspirate were sent for viral and bacterial culture and polymerase chain reaction assays. Quantitative studies for serum amino acids, urine organic acids, fatty acid oxidation substrates, and immunoglobulins were also performed.

The patient is admitted to the intensive care unit and requires mechanical ventilation. She is treated with broad-spectrum intravenous antibiotics, vasopressors, and extracorporeal membrane oxygenation.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

### Diagnosis

The infant's respiratory culture specimen from the endotracheal tube grew gram-positive bacilli without speciation and was presumed to be a contaminant. A repeat respiratory culture specimen again grew gram-positive bacilli that appeared unusual and was determined to be acid-fast bacilli. Cultures from broth Mycobacteria Growth Indicator Tubes were positive for *Mycobacterium tuberculosis*.

Social history revealed that the patient's parents are Ecuadorian and have family friends living with them. As part of the epidemiologic investigation, household contacts had tuberculin skin tests conducted. The child's mother is found to be positive, although there is no known active disease.

### Differential Diagnosis

For young infants past the immediate neonatal period, the differential diagnosis for a neonate who is experiencing respiratory failure and shock is broad. Systemic infections such as sepsis, meningitis, and pneumonia often present with shock and respiratory distress. Similarly, congenital heart disease, pertussis, influenza, and, rarely, myocarditis, endocrinopathies, and inborn errors of metabolism can lead to circulatory and respiratory collapse. Nonaccidental trauma must also be considered as a cause of shock.

As the results of laboratory studies returned, there was increasing suspicion for an unusual pathogen. Once *M tuberculosis* was identified, the patient was started on antituberculosis management of linezolid, isoniazid, pyrazinamide, rifampin, and amikacin, and she improved clinically.

### **The Condition**

A diagnosis of tuberculosis in this infant was confirmed by isolating the organism in culture. The diagnosis of congenital tuberculosis versus perinatal tuberculosis is difficult to establish clinically in this case. Because miliary disease presented at a young age and the incubation period for tuberculosis is usually longer than 1 week, the degree of disease in this child supports congenital acquisition. Nonetheless, Cantwell's criteria cannot be fully met without additional maternal and possible sick-contact information. Although it is known that the patient's mother had no evidence of active pulmonary tuberculosis, which supports congenital tuberculosis, perinatal infection is still possible because the status of placental and genital tract disease at time of delivery is unknown.

Congenital tuberculosis is rare. Fewer than 300 cases were reported in the world before 1984, and 170 cases were reported between 1946 and 2009. Since 1992, the overall incidence of tuberculosis in the United States has been decreasing. This trend is attributed to better control of HIV, which decreases subpopulations coinfecting with tuberculosis, as well as an increased focus on prevention and treatment of the disease. Risks for infection include a higher number of immigrants to the United States from tuberculosis-endemic areas, particularly India, China, Mexico, and Latin America, and a high degree of person-to-person contact.

The initial diagnostic criteria for congenital tuberculosis, based on autopsy findings, were proposed by Beitzke in 1935 and included isolation of *M tuberculosis* from the infant; the following factors were also included: (1) demonstration of a primary hepatic complex, (2) lesions identified within days of birth, or (3) exclusion of extra-uterine exposure. The revised Cantwell criteria of 1993 adapted the original criteria and included tuberculosis infection of the placenta or maternal genital tract, as well as the presence of postprimary hepatic granulomas.

During pregnancy, maternal tuberculosis bacteremia can lead to infection of the placenta or the genital tract. Congenital infection is acquired three ways: (1) transplacentally, with translocation of hematogenous mycobacteria through the placenta to the umbilical vein; (2) by aspiration or ingestion of infected amniotic fluid; or (3) by direct contact with the endometrial genital tract during delivery. Transplacental acquisition of tuberculosis leads to fetal formation of a primary hepatic complex with secondary hematogenous dissemination, while ingestion leads to a primary pulmonary or gastrointestinal tract infectious focus.

The distinction between congenitally and perinatally acquired tuberculosis may be unimportant, as the clinical management of the patient and mother are similar in both cases. Infants who have congenital tuberculosis usually present with signs and symptoms 2 to 3 days after birth. Signs and symptoms of congenital tuberculosis are varied and nonspecific. Symptoms of congenital tuberculosis include (in order of frequency of report) hepatosplenomegaly, respiratory distress, fever, lymphadenopathy, abdominal distention, and lethargy or irritability. Children can also present with respiratory failure, disseminated intravascular coagulation, and multisystem organ failure. Patients often do not improve with antibiotic treatment, and they frequently worsen.

The Mantoux tuberculin skin test has a high false-negative rate in the first few weeks of disease but can turn positive in 3 weeks (although it can take up to  $\geq 3$  months in the first year after birth). Interferon-gamma release assays, although approved for use in adults and older children, are not approved for use in infants and frequently produce indeterminate results.

To isolate mycobacteria for diagnosis and sensitivity determination from young children, early-morning gastric aspirates (obtained before the child becomes awake and active, and before eating) have the highest diagnostic yield. Typically, three aspirates are sent, one each on sequential mornings. In the diagnostic laboratory, samples are stained and inoculated into culture. Depending on the extent and location of disease, mycobacteria may also be isolated from endotracheal aspirates and from biopsy specimens of bone marrow, liver nodules, lymph nodes, CSF, peritoneal and pleural fluids, and occasionally from ear discharge. Rarely, mycobacteria may be isolated from urine and from nasopharyngeal secretions.

Imaging often yields nonspecific findings; however, miliary tuberculosis on chest radiography and multiple liver and spleen nodules on ultrasound and computed tomography scan can be found. Imaging-guided tissue biopsies of suspected liver granulomas or lymph nodes often assist in diagnosis.

Important in the diagnostic process of the infant who has suspected congenital tuberculosis is evaluation of the mother for unrecognized disease. During pregnancy, mothers typically lack symptoms; however, 95% of mothers of infants who have congenital tuberculosis are found to have active disease. In a recent case series of infants who were diagnosed with congenital tuberculosis, maternal infections were not recognized until after delivery in 70% of cases. Of the women diagnosed with tuberculosis, 25% were asymptomatic. Of mothers of infants who have congenital tuberculosis, almost one-half were diagnosed with tuberculosis after their infants' congenital tuberculosis was recognized.

## Management

Optimal treatment of congenital and perinatally acquired tuberculosis requires knowledge of the antimycobacterial susceptibilities of the infecting mycobacterium, as well as detailed assessment of the extent of disease. It also requires the guidance of a pediatric infectious diseases consultant who is experienced with such management.

Initial treatment of congenital or perinatal tuberculosis infection requires a multi-drug antituberculosis regimen. Initial regimens typically consist of isoniazid, rifampin, and pyrazinamide, with or without streptomycin. In cases in which resistant tuberculosis is possible, additional drugs may be added until susceptibility data are available. Typically, a 4- to 5-drug therapy regimen is given for at least 2 months, after which a regimen of isoniazid and rifampin is given.

Infants who have congenital tuberculosis are placed in respiratory isolation, not because the infant poses an infectious risk, but because there may be a parent or other adult who has active pulmonary disease.

## Prognosis

The mortality of congenital tuberculosis since 1994 is 33.9%; before 1994, it was 52.6%. This difference is likely due to earlier diagnosis and effective treatment. Factors that worsen prognosis include intracranial lesions, decreased or normal white blood cell levels, and patients presenting at younger than 3 weeks of age.

### **Lessons for the Clinician**

Early diagnosis of congenital tuberculosis is challenging. Congenital tuberculosis has varied and nonspecific signs and symptoms at the time of presentation. Imaging and other diagnostic studies may produce inconclusive results.

Congenital tuberculosis should be considered in an infant with shock or pneumonia who is unresponsive to standard antibiotics, especially in infants who have unexplained hepatosplenomegaly.

Multidrug antituberculosis regimens are safe and effective for the treatment of congenital tuberculosis.

## Acknowledgment

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*Susan M. Slattery, MD, Aaron J. Muller, MD, Kenneth Alexander, MD, PhD, and Joseph R. Hageman, MD, Comer Children's Hospital, Pritzker School of Medicine, University of Chicago, Chicago, IL, and NorthShore University HealthSystem, Evanston, IL*

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### COMMENTARY BY DR JOSEF NEU, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE

A recent review discusses diagnosis and therapies of this disease that is still with us: Saramba MI, Zhao D. A perspective of the diagnosis and management of congenital tuberculosis. *J Pathog*. 2016;8623825. doi:10.1155/2016/8623825

*Part 14*

# **Skeletal System**



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## **36-Week Male Infant With Skeletal Abnormalities**

### **Presentation**

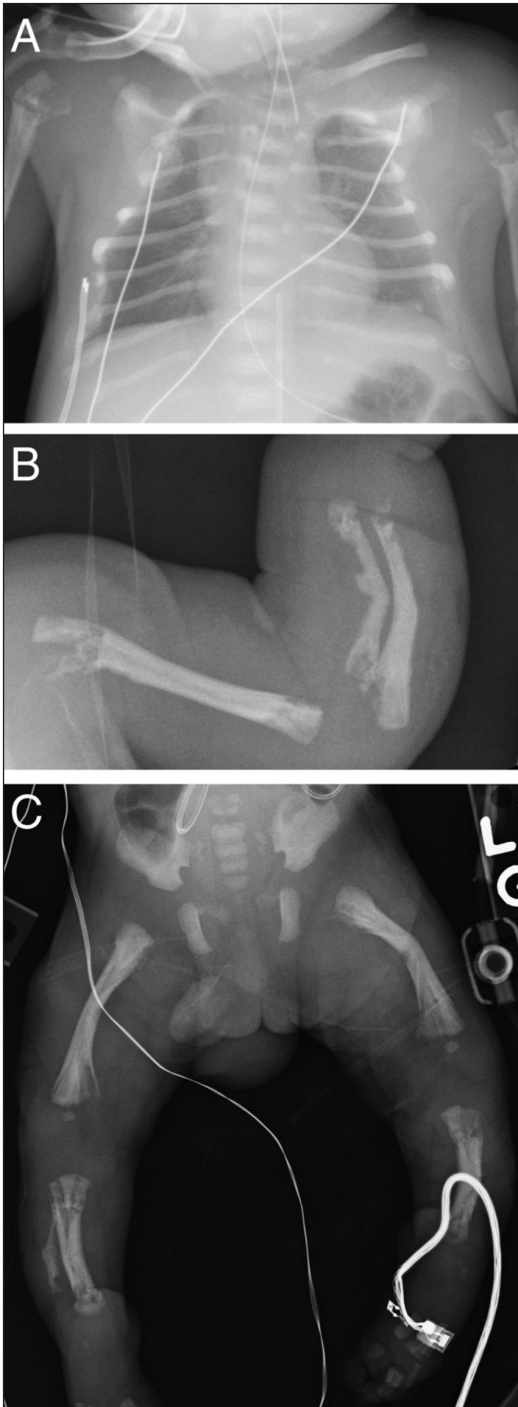
A male infant appropriate for gestational age is born at 36 weeks via induced vaginal delivery to a 28-year-old gravida 2 para 2 woman. Labor was induced early because of polyhydramnios and short, bowed long bones evident on fetal ultrasonography at 19 weeks' gestation. Other fetal findings on ultrasonography included bilateral talipes equinovarus and absent nasal bone; no intracranial abnormalities were identified. Fetal echocardiography performed at 19 weeks' gestation revealed no evidence of structural or functional cardiac abnormalities. The result of prenatal fluorescence in situ hybridization evaluation was negative for trisomy 13, 18, and 21. Other prenatal laboratory tests performed were comparative genomic hybridization microarray, which revealed no clinically significant imbalances, and  $\alpha$ -fetoprotein measurement, which revealed a level that was 0.7 multiple of the median (reference range, <2.0 multiple of the median).

At birth, the infant has poor respiratory effort and requires intubation and mechanical ventilation. Apgar scores are 5 and 6 at 1 and 5 minutes, respectively. Physical examination findings are significant for widely split cranial sutures, soft skull bones, facial bruising, excessive plantar flexion of both feet, and contractures of all 4 extremities. Skin dimples are present in all 4 distal extremities (Figure 52.1).



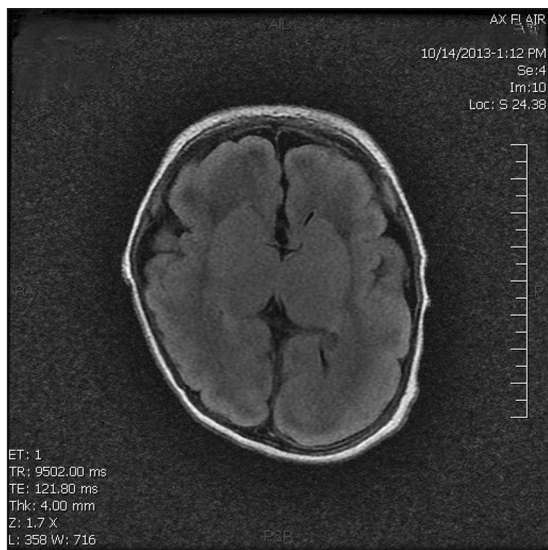
**Figure 52.1.** Infant with skeletal dysplasia with bowing and contractures of the extremities and excessive plantar flexion of the feet.

By 24 hours after delivery, the infant begins breathing spontaneously and is weaned to room air. Skeletal survey findings reveal decreased bone mineralization, particularly in the skull, and diffuse metaphyseal dysplasia with bowing deformity in the extremities, radial spurs, and dysplastic ribs (Figure 52.2). Echocardiography results are negative for structural or functional cardiac disease, and renal ultrasonography reveals mild dilatation of the intrarenal collecting system bilaterally. Laboratory evaluation is significant for the following: alkaline phosphatase, less than 20 U/L (reference range, 38–405 U/L); ionized calcium, 6.0 mg/dL (1.5 mmol/L) (reference range, 4.48–5.28 mg/dL [1.12–1.32 mmol/L]); phosphorous, 6.1 mg/dL (1.97 mmol/L) (reference range, 3.6–8.2 mg/dL [11.15–25.39 mmol/L]); vitamin D<sub>2</sub> (1,25 dihydroxyvitamin D), less than 8 pg/mL (<21 pmol/L) (reference range, 31–87 pg/mL [81–226 pmol/L]); and parathyroid hormone intact, 14 pg/mL (14 ng/L) (reference range, 8–72 pg/mL [8–72 ng/L]).



**Figure 52.2.** A. Chest radiograph of infant showing small, short ribs with irregular shape. B. Upper extremity showing short, bowed extremity with metaphyseal hypomineralization. C. Lower extremities showing severe hypomineralization with short, bowed long bones.

Because of a family history of a sibling with a Chiari malformation and hydrocephalus that required ventriculoperitoneal shunting, the patient undergoes brain magnetic resonance imaging. Findings reveal a very immature and simplified gyral pattern with decreased and shallow sulci (Figure 52.3). Also identified are several foci of restricted diffusion in the right and left parieto-occipital regions (left greater than right), suggesting small acute infarcts. Subsequently, electroencephalography reveals sharp transient activity in all 4 quadrants but no definable epileptiform activity.



**Figure 52.3.** Immature and simplified gyral pattern with decreased and shallow sulci on magnetic resonance imaging.

An analysis of urine organic acids reveals an elevated phosphoethanolamine level. Vitamin B<sub>6</sub> profile reveals an elevated pyridoxal 5-phosphate level of 431 mcg/L (reference range, 5–50 mcg/L).

By day 3, the infant's condition deteriorates, characterized by worsening apnea and bradycardia. On day 7, he is given do not resuscitate status at the parents' request. He dies on day 13 after a severe apneic episode.

*Take a moment to consider the diagnosis in this infant.*

## Discussion

### *Diagnosis*

Subsequently, a serum sample is sent for molecular testing to confirm hypophosphatasia. The result is positive. Infants who are identified on fetal ultrasonography as having skeletal abnormalities are challenging medical cases for pediatricians and geneticists. In addition, the infant in this case had severe respiratory depression at birth and required resuscitation with mechanical ventilation, complicating the clinical course. The infant also had laboratory findings of a markedly low alkaline phosphatase concentration and an elevated serum calcium concentration and was diagnosed as having hypophosphatasia once molecular test results were positive.

### *The Condition*

Hypophosphatasia is an illness of decreased bone or teeth mineralization with associated low alkaline phosphatase activity. It has a wide range of clinical presentation due to variations in the underlying cause. Complications, such as dental disease, skeletal demineralization, hypercalcemia, bone fractures, and craniosynostosis, are common. There is a perinatal type, which our infant had; this type often presents in utero with poor skeletal mineralization and shortened long bones on prenatal ultrasonography. After birth, affected infants have fragile bones with distinct radiographic findings (Figure 52.2) that reveal decreased mineralization and low alkaline phosphatase levels. Low levels of alkaline phosphatase can help distinguish this disorder from similar diseases, such as rickets, renal osteodystrophy, osteogenesis imperfecta, or other chondrodysplasias.<sup>1</sup> Perinatal hypophosphatasia can be lethal because of respiratory insufficiency or benign with only skeletal abnormalities, with the affected infant progressing to a less severe infantile form of hypophosphatasia. The infantile form presents by age 6 months with symptoms of rickets but without elevation in alkaline phosphatase level. The childhood form presents similarly with poor bone mineralization and unexplained fractures. In adulthood, hypophosphatasia may present with early loss of dentition and stress fractures. In general, the earlier the onset of hypophosphatasia, the more severe the disease process.

Hypophosphatasia has been attributed to low levels of tissue-nonspecific alkaline phosphatase (TNSALP), which is encoded by the *ALPL* gene on chromosome 1. The disease is inherited in either an autosomal recessive or dominant fashion, although the recessive form typically produces a more severe phenotype. Many cases have also been found to be compound heterozygotes. To date, there have been more than 270 distinct mutations described.

Without a functioning TNSALP, phosphate and vitamin B<sub>6</sub> build up extracellularly, which can be detected in the serum and urine. Important to the pathophysiology of hypophosphatasia is the extracellular accumulation of inorganic pyrophosphate,

which is known to suppress the formation of hydroxyapatite crystals and lead to defective bone mineralization. In addition, the resultant hypercalcemia or the lack of intracellular vitamin B<sub>6</sub> (a cofactor in  $\gamma$ -aminobutyric acid synthesis) may be responsible for the increase in seizure activity seen in patients with hypophosphatasia. Hypercalcemia and the lack of vitamin B<sub>6</sub> become clinically important because patients with hypophosphatasia are at higher risk for pyridoxine-responsive seizures, and vitamin B<sub>6</sub> should be the first-line treatment for seizures in these infants.

## **Management**

Although there is no formal treatment for hypophosphatasia, symptomatic treatment has been effective for the nonlethal forms. Girschick et al<sup>2</sup> described the symptomatic pain relief of 7 children with childhood hypophosphatasia treated with nonsteroidal anti-inflammatory drugs. In addition, the recombinant human parathyroid hormone teriparatide has been reported to have positive effects on pain and bone healing in a woman with hypophosphatasia and a spontaneous proximal femur fracture.<sup>3</sup> Teriparatide therapy appeared to increase levels of TNSALP while decreasing levels of extracellular inorganic phosphate. However, teriparatide is relatively contraindicated in the pediatric population because of the increased risk of osteosarcoma when used in patients with open epiphyses.

Future treatment of hypophosphatasia may focus on repletion of TNSALP rather than only alleviating the disease symptoms. In 2003, Whyte et al<sup>4</sup> described an 8-month-old girl with the severe infantile form who was given T-cell-depleted, haploid-matched bone marrow with a “stromal cell boost” at age 21 months. Although the biochemical abnormalities found in hypophosphatasia were never fully corrected, the skeletal metabolism greatly improved, and the therapy was believed to have rescued the girl. More recently, Whyte et al<sup>5</sup> used a bone-targeted recombinant human TNSALP (ENB-0040) to treat 11 patients with life-threatening or debilitating infantile or childhood hypophosphatasia. Whyte et al<sup>5</sup> noted marked improvement in skeletal radiographs, developmental milestones, and pulmonary function, giving a positive outlook on the future therapy for this debilitating disease.

Routine surveillance of these children includes twice yearly dental visits starting at age 1 year. Close monitoring and attention to signs of increased intracranial pressure due to craniosynostosis are also important. Parents should be advised to avoid bisphosphonates and excess vitamin D in these infants as well.

## Lessons for the Clinician

Hypophosphatasia should be included in the differential diagnosis for skeletal dysplasia.

Laboratory abnormalities in hypophosphatasia include a severely low alkaline phosphatase level, hypercalcemia, and an elevated urine phosphoethanolamine level.

The earlier the onset of hypophosphatasia, the more severe the disease process.

Health maintenance with close monitoring for craniosynostosis is important.

*Christina Tryon, MD, Jennifer Reed, MD, David Somsen, MSIV, Suzanne Reuter, MD, Sanford School of Medicine at the University of South Dakota, Sioux Falls, SD*

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## COMMENTARY BY DR DARA BRODSKY, BETH ISRAEL DEACONESS MEDICAL CENTER

Approximately 300 distinct mutations in the *ALPL* gene are currently known, and pre-natal genetic diagnosis is now possible for at-risk fetuses. In 2016, children with hypophosphatasia who were treated with asfotase alfa (bone-targeted recombinant human TNSALP) were followed for 5 years and had improved bone health and decreased pain with minimal side effects. This drug is now available for pediatric-onset hypophosphatasia.<sup>1</sup> There is a hope that a cure for this disease might be possible by using gene therapy to deliver alkaline phosphatase.

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# Challenging Cases in Neonatology

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